The Relation of Portal Cirrhosis to Hemochromatosis and to Diabetes Mellitus

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This study is based upon 932 cases of clinical portal cirrhosis from the autopsy service at the University of Minnesota. It includes all the cases of this disease recorded during the forty-four year period 1911 through 1953. No cases of obstructive biliary cirrhosis or acute necrosis of the liver are included.

Portal cirrhosis is not a sharply defined entity, since a moderate increase of portal connective tissue is frequently seen at autopsy in subjects who had no clinical signs of liver disease. In this discussion only those cases are considered in which the cirrhosis or one of its complications was the major cause of death, and in which a grossly cirrhotic liver was found at autopsy. Microscopic sections of the liver were available in 733 of the 932 cases, and these all showed a convincing increase of portal fibrous tissue. In nearly all instances the increase of portal connective tissue was striking (grade 3), but in a few it was moderate (grade 2). No cases of mild portal cirrhosis (grade 1) are included.

Incidence of Portal Cirrhosis. Herbut and Tamaki[1] found 115 cases of cirrhosis in 6,000 necropsies (1.9 per cent); Boles,[2] 142 in 3,637 necropsies (3.9 per cent); and Hall and associates,[3] 782 in 16,600 necropsies (4.7 per cent). These authors did not give the age distribution of their material. Reinberg and Lipson[4] reported cirrhosis in 5.9 per cent of adults at necropsy. In our autopsies (table 1) the incidence in all subjects over forty years of age is 1.7 per cent. Age has an important influence on the statistics, since cirrhosis is over three times as frequent in persons past the age of forty as in those dying before that age (table 1). The discrepancies in autopsy statistics may be due in part to the source of the material, or they may be attributable to different criteria for the diagnosis. Those who include mild subclinical cirrhosis will naturally obtain a higher incidence than those who restrict the diagnosis to clinical cases.

Sex. Douglass and Snell[5] in a clinical study of 444 cases found the ratio of males to females was 3.5 to 1. Ratnoff and Patek[6] in a clinical study of 386 cases found a ratio of 2 to 1. This is a much higher ratio than that obtained in autopsy material when correction is made for the smaller number of females. Boles[2] found a ratio of 5 to 4, and Hall[3] one of 4 to 3. In our autopsies the preponderance of males is too small to be significant.

For purposes of study the cases exhibiting any degree of hemosiderosis of the liver have been arranged in several groups. This part of the study is based upon the 733 cases in which microscopic sections of the liver were available.

Group 1. Typical Bronze Diabetes. The eleven cases listed in table 2 presented the complete syndrome of bronze diabetes, namely severe portal cirrhosis with marked hemosiderosis of the liver, diabetes mellitus, and melanoderma. The duration of the disease, as indicated by the pigmentation of the skin, varied from five months to over thirty years. The known duration of the diabetes varied from five months to four years. In four subjects the diabetes was mild and easily controlled; in four it was severe, and three of these died in diabetic coma.

In two subjects, Numbers 10 and 11, bronze diabetes developed during the course of a refractory anemia. It will be noted that 187 units of blood were given to patient 10, but only 3 units to patient 11. A notable feature of this group is the complete absence of hyaline islets and complete or almost complete degranulation of the beta cells in all instances.

Bronze diabetes is a rare disease. Marble and Bailey[7] found 30 proven and 17 probable cases among 30,000 diabetics (0.16 per cent), and Boulin[8] 70 among 4,226 diabetics (1.66 per cent). In our autopsies there are 11 cases among 1,700 diabetics (0.65 per cent). Some writers seem to restrict the diagnosis of hemochromatosis to bronze diabetes (Marble and Bailey, Boulin), but a majority do not insist upon the complete syn-

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TABLE 1
Incidence of clinical portal cirrhosis in autopsies

	Males			Females		
Age, years	No. of autopsies	No. of cases of cirrhosis	Per cent of cirrhosis	No. of autopsies	No. of cases of cirrhosis	Per cent of cirrhosis
0-40	12,956	76	0.51	9,479	45	0.47
40-90	31,752	557	1.75	15,618	254	1.62
0-90	44,708	633	1.42	25,097	299	1.19

TABLE 2
Group 1. Typical bronze diabetes

Serial no.	Age, years	Sex	Severity of diabetes*	Hyaline islets	Beta granules†	Comment
1	65	F	3	0	1-	Diabetic coma
2	56	M	3	0	1	Diabetic coma
3	54	M	3	0	0	Myocardial hemosiderosis
4	62	M	2	0	1-	Malignant hepatoma
5	57	M	3	0	0	Diabetic coma
6	66	M	1	0	1-	Malignant hepatoma
7	62	M	1	0	1-	Cirrhosis
8	57	M	2	0	0	Cirrhosis
9	55	M	1	0	1-	Cirrhosis
10	65	M	2	0	0	Refractory anemia, 4 yrs. 187 units of blood
11	55	M	1	0	0	Refractory anemia, 22 yrs. 3 units of blood

*Severity of diabetes based on insulin requirement: 1 indicates control without insulin; 2 indicates requirement of a dosage of insulin up to 30 units per day; and 3, a requirement of 30 units or more.
†Beta granules: 0 indicates no granules; 1-, a very few; 1, a definite reduction; and 2 and 3, normal granulation.

drome for the diagnosis of hemochromatosis.

Group 2. Diabetic Hemochromatosis Without Melanoderma. It has long been appreciated, especially by pathologists, that pigmentary cirrhosis may occur in association with diabetes mellitus without conspicuous pigmentation of the skin. In such cases the clinician does not hesitate to make a diagnosis of hemochromatosis when pigmentary cirrhosis is demonstrated at autopsy or by needle biopsy of the liver. Eighteen cases of this type are listed in table 3. It is possible that a biopsy of the skin would have revealed hemosiderin in some of these, but they cannot be regarded as typical examples of bronze diabetes.

Melanoderma. The bronze or dark pigmentation of the skin in hemochromatosis is due to an accumulation of melanin in the deep layers of the epidermis. Biopsies of the pigmented skin usually reveal a few hemosiderin granules around the small blood vessels in the corium. This is of diagnostic value, but the amount of hemosiderin is insufficient to affect the color of the skin. The dark color is due to melanin in the epidermis. Melanotic pigmentation of the skin, similar to that of hemochromatosis, occurs in other conditions, notably Addison's disease, neurofibromatosis, and Hodgkin's disease.

In publications dealing with hemochromatosis, melanoderma is sometimes described as the first sign of the disease (Knutsen[9]), sometimes as a late manifestation or an unessential feature (Chesner[10]). Its frequency in hemochromatosis seems to depend upon how the diagnosis is established. Naturally it is less frequent in a series in which the diagnosis is made by autopsy or liver biopsy than in one in which the diagnosis is based upon the clinical features. Sheldon[11] in an extensive survey of the early literature found melanoderma in 83.8 per cent, but this high incidence is presumably due to the tendency of authors to report only convincing cases. In autopsy material melanoderma is an infrequent feature of hemochromatosis.

The eighteen subjects listed in table 3 all had diabetes and severe portal cirrhosis, but the degree of hemosiderosis of the liver varied from severe (grade 3) to mild (grade 1). Whether the five cases with mild hemosiderosis (Numbers 25 to 29) are true examples

TABLE 3
Group 2. Diabetic hemochromatosis without melanoderma

Serial no.	Age, years	Sex	Severity of diabetes*	Degree of hemosiderosis of liver	Hyaline islets	Beta granules†	Comment
12	57	M	2	3	0	1	
13	78	M	1	3	1	3	
14	55	M	3	3	—	—	
15	79	M	3	3	3	1	
16	52	M	1	3	0	3	
17	64	M	2	3	3	2	
18	60	M	2	2	—	—	
19	66	F	2	2	0	3	
20	71	M	1	2	1	2	
21	57	M	1	2	0	3	
22	57	M	2	2	0	2	1 unit of blood
23	60	M	1	2	0	1–	5 units of blood
24	47	M	2	2	0	0	
25	50	M	1	1	0	1	
26	59	M	1	1	0	3	
27	76	M	1	1	0	3	
28	63	M	2	1	0	2	
29	89	F	1	1	0	2	

*Severity of diabetes based on insulin requirement: 1 indicates control without insulin; 2 indicates requirement of a dosage of insulin up to 30 units per day; and 3, a requirement of 30 units or more.
†Beta granules: 0 indicates no granules; 1-, a very few; 1, a definite reduction; and 2 and 3, normal granulation.

of hemochromatosis depends upon one's definition of the disease. The causes of death were as follows: cirrhosis, eight cases; infection, five; malignant hepatoma, 2; fracture of femur, 1; mitral stenosis, one; and coronary thrombosis, one case. There were hyaline pancreatic islets in only four of sixteen cases, and beta cell degranulation in four of sixteen.

Group 3. Severe Cirrhosis with Varying Degrees of Hemosiderosis of the Liver. No Clinical Diabetes but Hyaline Islets in the Pancreas. The eight subjects listed in table 4 had no glycosuria or other clinical signs of diabetes, but there are no data on the fasting blood sugar or the glucose tolerance. However, they show hyaline islets in the pancreas suggesting diabetes. In Numbers 32 and 35 there is also a rather marked degranulation of the beta cells. All had severe portal cirrhosis, and Number 31 had melanoderma. However, the degree of hemosiderosis of the liver varies from grades 1 to 3. These are probably cases of diabetic hemochromatosis, but they have not been treated as such in the analyses, since some pathologists do not consider hyaline islets sufficient evidence of diabetes.

Group 4. Nondiabetic hemochromatosis. There remain for consideration 186 cases of pigmentary cir-

TABLE 4
Group 3. Severe cirrhosis. No clinical diabetes but hyaline islets in the pancreas

Serial no.	Age	Sex	Degree of hemosiderosis of the liver	Hyaline islets	Beta granules*	Comment
30	52	M	3	1	3	
31	54	M	3	1	—	Melanoderma
32	74	M	3	1–	1	
33	69	M	2	1	3	
34	72	M	2	1	2	3 units of blood
35	59	M	1	1	1	
36	64	M	1	1	2	
37	57	M	1	2	2	

*Beta granules: 0 indicates no granules; 1–, a very few; 1, a definite reduction; and 2 and 3, normal granulation.

rhosis without diabetes in which there is minimal to maximal hemosiderosis of the liver. These have been arranged in four subgroups in accordance with rough estimations of the amount of iron demonstrable in microscopic sections of the liver. The iron granules were always in the parenchymal cells and frequently in the portal fibrous tissue also. The few cases in which iron was found only in the reticuloendothelium have not been tabulated. Grade 3 refers to cases in which there is abundant iron in every lobule and frequently in the portal tissues also (figure 1). In grade 2 hemosiderosis there is a moderate amount of iron in most of the lobules, but a few are free of iron. In grade 1 hemosiderosis there is a moderate amount of iron in a few of the lobules, but most of them contain no iron (figure 2). There may be a little iron in the portal tissues. Grade 1— refers to cases with a minimal iron deposit in an occasional lobule. When only a small amount of iron is present it is limited to the peripheries of the lobules.

In table 5 the cases of simple or nondiabetic hemochromatosis are arranged with respect to age and sex and the degree of hemosiderosis of the liver. All had severe portal cirrhosis.

The 28 cases with grade 3 hemosiderosis of the liver would generally be accepted as examples of hemochromatosis. Six subjects had melanoderma, and marked hemosiderosis was found in the fourteen pancreases examined. No patient had glycosuria, but there are no observations on fasting blood sugar or glucose tolerance. Five of eleven subjects in whom pancreatic tissue was available showed beta cell degranulation, which is presumptive evidence of diabetes. Possibly a latent diabetes could have been demonstrated in some of these subjects.

There are 57 subjects with grade 2 hemosiderosis of the liver. Hemosiderosis of the pancreas was found in 20 of 28 cases in which the pancreas was stained for iron, and frequently the pigmentation was more intense in the pancreas than in the liver. A liver biopsy from any one of these subjects would have been interpreted as hemochromatosis if stained for iron. There was no instance of melanoderma or glycosuria, and only one of 39 pancreases examined showed beta cell degranulation. Probably a majority of pathologists would accept

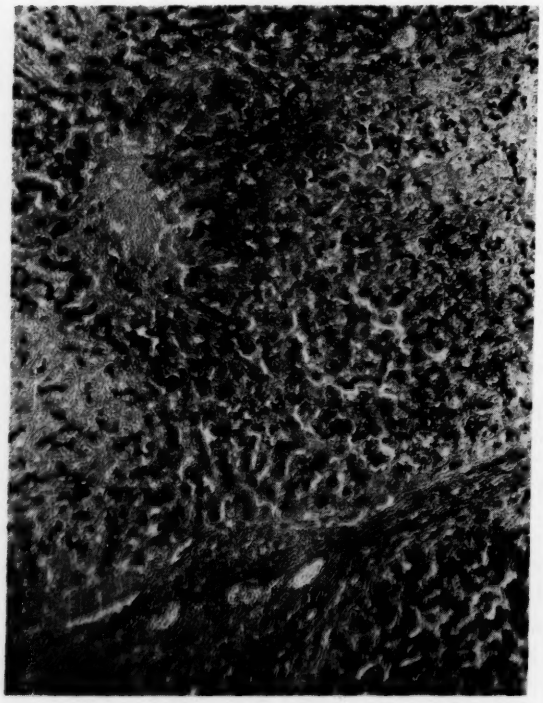

FIG. 1. Grade 3 hemosiderosis of the liver. The liver cells throughout the lobules are filled with hemosiderin. Photomicrograph.

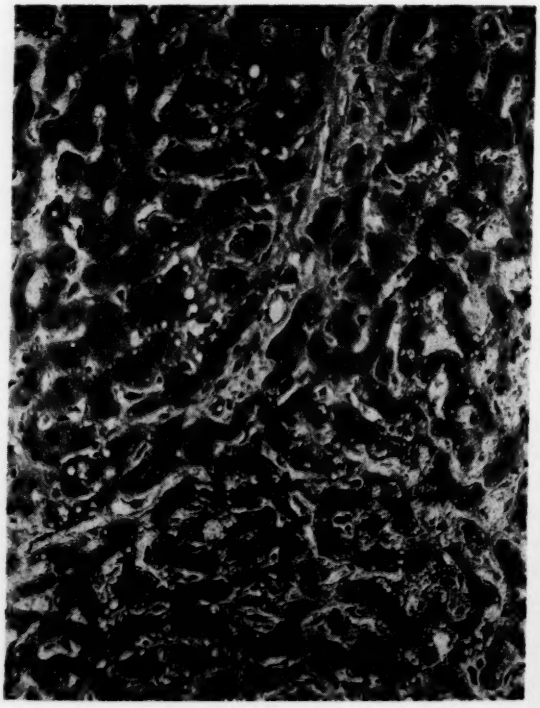

FIG. 2. Grade 1 hemosiderosis of the liver. A moderate amount of hemosiderin is present, especially in the peripheries of the lobules. Photomicrograph.

TABLE 5

Age and sex distribution of the different forms of pigmentary cirrhosis and of nonpigmentary cirrhosis

Diabetic hemochromatosis			Nondiabetic hemochromatosis: degree of hemosiderosis								Nonpigmentary cirrhosis	
			3		2		1		1—			
Age, Years	M	F	M	F	M	F	M	F	M	F	M	F
0-30	0	0	0	0	0	0	0	2	2	2	17	18
30-60	14	0	12	2	24	4	31	8	13	6	219	108
60-90	12	3	11	3	20	9	18	10	7	2	97	48
Total	26	3	23	5	44	13	49	20	22	10	333	174

this group as hemochromatosis.

There are 69 cases with mild hemosiderosis of the liver (grade 1). A needle biopsy of the liver would not be interpreted as hemochromatosis unless a pigmented area were secured. There was no instance of melanoderma or glycosuria. There was iron in 11 of 19 pancreases that were stained, and in 2 instances there was as much iron as is found in bronze diabetes. It is evident that this group differs from typical hemochromatosis only in the degree of hemosiderosis of the liver.

There are 32 cases in which only traces of iron were found in the liver. It is unlikely that a needle biopsy would have secured a pigmented area. No patient exhibited glycosuria or melanoderma.

In 507 (69.3 per cent) of the 733 cases examined microscopically there was no hemosiderin in the liver. It is clear that cases of portal cirrhosis with mild hemosiderosis of the liver differ only in degree from those which we are accustomed to call hemochromatosis. Any classification of pigmentary cirrhosis based upon the amount of iron in the liver is arbitrary and indefinite.

This blending of hemochromatosis with ordinary portal cirrhosis has been previously recognized by others. Yater and associates[12] noted that considerable amounts of iron pigment may be found in ordinary portal cirrhosis. Herbut and Tamaki[1] described transitions between hemochromatosis and simple portal cirrhosis. Hedinger[13] mentioned cirrhosis with incomplete pigmentation. It appears that there are many intermediary stages between nonpigmented portal cirrhosis and fully developed bronze diabetes. Nondiabetic hemochromatosis blends with ordinary portal cirrhosis. The entire group of pigmentary cirrhoses will now be discussed.

Age. Sheldon,[11] whose review deals largely with diabetic hemochromatosis, found no subject under twenty years of age. Only one of our 29 subjects with diabetic hemochromatosis was under fifty years of age. Most of the reported cases are those of patients past middle life.

There are few data in the literature on simple, or nondiabetic, hemochromatosis. Our cases, listed in table 5, indicate that simple hemochromatosis appears somewhat earlier in life than the diabetic form, and many of those with mild hemosiderosis are relatively young. This feature suggests that pigmentation increases with age.

Sex. The literature shows a great preponderance of males in diabetic hemochromatosis. Sheldon's[11] review included 298 males and 13 females; Butt and Wilder,[14] 29 males and 1 female; Marble and Bailey,[7] 44 males and 3 females; Boulin,[8] 59 males and 11 females; Althausen,[15] 20 males and 3 females. Twenty-six of our 29 subjects with diabetic hemochromatosis were males (table 5).

There is little detailed information in the literature as to the sex distribution of nondiabetic hemochromatosis. The sex incidence of the different degrees of hemosiderosis is shown in table 5. In making comparisons one should double the number of females, since there are approximately twice as many males as females in the autopsy population of these ages. In grade 3 hemosiderosis, which anyone would accept as hemochromatosis, the ratio of males to females is 2 to 1, a much lower ratio than prevails in diabetic hemochromatosis. In grade 2 hemosiderosis the ratio is about 3 to 2; and in those with mild and very mild hemosiderosis (grades 1 and 1—) the sex distribution is approximately equal. These observations suggest that pigmentary cirrhosis develops as frequently in females as in males but does not progress to a severe degree so often.

The Frequency of Hemosiderosis of the Liver in Portal Cirrhosis. Summarizing the data in tables 4 and 5 there was some degree of hemosiderosis of the liver in 173 of 506 males (34.2 per cent) and 52 of 226 females (23.0 per cent) with clinical portal cirrhosis. The frequency of hemosiderosis in cirrhotic livers in-

creases with age. In males the incidence is 21.7 per cent in those below fifty years of age and 40 per cent in those over fifty. In view of numerous intermediary stages it appears highly probable that cirrhotic livers with mild hemosiderosis represent an early stage of the disease we are accustomed to call hemochromatosis. The initial disease in hemochromatosis is portal cirrhosis.

The Relation of Portal Cirrhosis to Diabetes Mellitus. There is no evidence that diabetics are prone to develop portal cirrhosis. Frankel[16] found 36 cases of cirrhosis in 3,543 diabetics; Wilder,[17] 17 in 2,584 diabetics; Joslin,[18] 52 in 10,235 diabetics; and Feldman and Feldman,[19] 4 in 37 diabetics. This gives an incidence of 0.5 to 1 per cent, which is less than the incidence of cirrhosis in the nondiabetic population.

However, our problem is to determine whether diabetes develops more frequently in cirrhotics than in noncirrhotics. Robert[20] reported diabetes in 2.4 per cent of noncirrhotics and 7.6 per cent of 115 cirrhotics. Ratnoff and Patek[6] found that 5 per cent of 386 cirrhotics had diabetes, and Reinberg[4] noted diabetes in 4.4 per cent of 777 cirrhotics. Feldman and Feldman[19] concluded that diabetes is as frequent in noncirrhotics as in cirrhotics. From the literature this conclusion appears justified, but the material presented has not been analyzed with respect to sex, and cases of diabetic hemochromatosis are usually excluded.

In table 6 the incidence of diabetes in the general autopsy population is compared with its incidence in subjects with portal cirrhosis. The cases with hyaline islets but without clinical diabetes have not been included as diabetics, but diabetic hemochromatosis is listed as diabetes developing in a cirrhotic. Diabetes is about five times as frequent in cirrhotic males as in the general autopsy male population. However, it appears that there is no striking increase of diabetes in cirrhotic females.

One obvious factor in the increased incidence of diabetes in cirrhotic males in our autopsies is that diabetic hemochromatosis, which occurs chiefly in males, is included. It will be noted, however, that even when the 26 males with diabetic hemochromatosis are omitted the incidence of diabetes is still three times as high in cirrhotic males as in the general autopsied male population. Some writers, in estimating the incidence of diabetes in cirrhotics, have omitted cases of frank hemochromatosis, apparently on the assumption that cirrhosis and hemochromatosis are separate entities. But if we are to determine the incidence of diabetes in cirrhotics there is no sound reason for excluding those cirrhotics who have hemosiderosis of the liver.

TABLE 6

The incidence of diabetes in the autopsy population compared with its incidence in portal cirrhosis

Age, years	No. of autopsies	Per cent diabetic	No. of cases of cirrhosis	Per cent diabetic
		Males		
0-40	12,956	0.65	76	4.0
40-90	31,752	2.32	557	11.8
		Females		
0-40	9,479	1.04	45	2.0
40-90	15,618	4.98	254	6.7

In table 7 the degree of hemosiderosis of the liver is indicated in 61 males and 16 females, with both cirrhosis and diabetes, in whom microscopic sections of the liver were available. Thirty-five of the 61 males and 13 of the 16 females had no hemosiderosis of the liver. The fact that such a large proportion of the cases of diabetes develop in nonpigmentary cirrhosis indicates that pigmentation of the liver or pancreas is not the cause of the diabetes. The cause of the increased frequency of diabetes in cirrhotic males is obscure, but the diabetes is probably a manifestation of the underlying hepatic disease and not an effect of the hemosiderosis.

TABLE 7

Degree of hemosiderosis of the liver in subjects with portal cirrhosis and diabetes mellitus

Degree of hemosiderosis	No. of males	No. of females
0	35	13
1–	0	0
1	4	1
2	7	1
3	15	1
	61	16

The incidence of diabetes in frank hemochromatosis is high. It was present in 70 per cent of Sheldon's[11] series. Stauffer[21] found diabetes in 12 of 27 cases; Butt and Wilder[14] in 26 of 30 cases; and Althausen[15] in 18 of 23 cases. Obviously, however, the frequency of diabetes depends upon how the cases are selected. Cases without diabetes or melanoderma are apt to be overlooked. The relation of diabetes to the degree of hemosiderosis is given in table 8. There is a significant increase in the incidence of diabetes in those with grade 3 hemosiderosis, but diabetes is about as frequent in nonpigmentary cirrhosis as in cirrhosis with mild to moderate hemosiderosis. Apparently those with severe hemosiderosis are more apt to have diabetes, but no clear relation between diabetes and hemosiderosis can

TABLE 8

Relation of diabetes to the degree of hemosiderosis of the liver

Degree of hemosiderosis	No. of cases of cirrhosis	No. of diabetics	Per cent diabetic
Nonpigmentary cirrhosis	333	35	10.5
Grade 1–	22	0	0.0
Grade 1	57	5	8.8
Grade 2	52	8	15.4
Grade 3	40	16	40.0

be established.

Diabetes is usually a late manifestation of those cases of hemochromatosis that begin with melanoderma. Frequently a high fasting blood sugar or a decreased glucose tolerance may be demonstrated before the onset of glycosuria. The diabetes is usually not difficult to control, but occasionally a very refractory case is encountered. The vascular lesions and the changes in the islets of Langerhans will be discussed later.

Hemosiderosis of Organs other than the Liver in Portal Cirrhosis. The pancreas is always heavily pigmented in bronze diabetes. In simple hemochromatosis with grade 3 hemosiderosis of the liver the pancreas was heavily pigmented in 5 of the 6 pancreases that were stained for iron. In grade 2 hemosiderosis of the liver the pancreas had mild to severe pigmentation in 20 of 28 cases. In 7 of these there was more pigment in the pancreas than in the liver. In the group with grade 1 hemosiderosis of the liver there was pigmentation of the pancreas in 11 of the 19 cases examined, and in 2 of these it was as pronounced as in bronze diabetes. The hemosiderin is nearly all in the acinar tissue, but occasionally there are a few granules in the islets. The pigmentation of the islets is never heavy enough to suggest an interference with their function.

The spleen usually shows only a mild hemosiderosis, much less pronounced than in the liver, unless the patient has been given blood transfusions.

Rarely, severe hemosiderosis of the myocardium causes death from cardiac failure (Swan,[22] Bothwell,[23] our case 3). No systematic study of hemosiderosis of other organs was made, but occasional observations show pigmentation of the adrenals and parathyroids. In one instance an iron deposit was noted in an atheromatous plaque in a coronary artery.

The Effect of Blood Transfusions in Portal Cirrhosis. In subjects that were given blood transfusions because of their anemia, one might believe that hemolysis of the transfused red cells was responsible for the hemosiderosis. To study this problem all of the subjects who received blood transfusions were assembled. There were 63 males and 35 females who received blood transfusions during the last few months of life. Sixteen of the 63 males (25 per cent) showed some degree of hemosiderosis of the liver; the incidence in 410 males who received no transfusions was 36 per cent. Only 2 of the 35 females had hemosiderosis of the liver; the incidence in 172 females who received no blood transfusions was 24 per cent. The usual transfusion was one to five units of blood, but some received more. One female who received 200 units during the last eight months of life and one male who was given 48 units during the last fifteen months had no hemosiderosis. Two subjects with grade 3 hemosiderosis received one and three units, respectively, during the last week of life. Since hemosiderosis was more frequent in those who were not transfused, there is no reason to attribute the hemosiderosis to the few transfusions that were given. However, repeated blood transfusions over a long period do cause massive generalized hemosiderosis.

The Effects of Repeated Blood Transfusions Over Long Periods. The usual effect of repeated blood transfusions in patients with chronic anemia is a massive hemosiderosis of the liver, spleen, pancreas, and various other organs without the development of portal cirrhosis or diabetes. However, in some instances a typical pigmentary cirrhosis develops, and rarely this is accompanied by diabetes (table 2, No. 10). Wyatt and Goldenberg,[24] in 3 cases of refractory anemia treated by transfusions, noted a mild cirrhosis in one. Wyatt, Mighton and Moragues[25] found some degree of cirrhosis in 5 of 8 cases of anemia treated with multiple transfusions. In one instance the cirrhosis was severe. Norris and McEwen,[26] in a patient with aplastic anemia who was given 100 transfusions, noted massive hemosiderosis and diabetes but no cirrhosis. Cottier[27] observed cirrhosis in one of two cases of panhematocytopenia treated with transfusions. Graef[28] reported hemochromatosis in one case of refractory anemia treated by transfusions, but 5 other cases similarly treated did not develop it. Mackey[29] found pigmentary cirrhosis in a subject with aplastic anemia who had been given 39.8 liters of blood over a period of three and one-half years. Schwartz and Blumenthal[30] found some degree of cirrhosis in 4 of 5 cases of anemia treated by transfusions. One patient developed diabetes. Aufderheide and associates[31] reported two cases of pigmentary cirrhosis following repeated transfusions, and one of these patients had typical bronze diabetes (table 2, No. 10).

The fact that hemochromatosis may develop in anemic patients treated with multiple blood transfusions has led to the view that the hemosiderosis produced by the transfusions is the cause of the portal cirrhosis. But there are several reports in the literature of patients with chronic anemia who developed hemochromatosis although no blood transfusions were given. Bomford and Rhoads[32] noted pigmentation of the skin in 6 of 30 cases of refractory anemia; one of these developed diabetic hemochromatosis and two others showed hemochromatosis at autopsy. Houston's[33] patient, who had macrocytic anemia for over thirty years, developed bronze diabetes. Zeltmacher[34] observed severe pigmentary cirrhosis at autopsy in a man who had had aplastic anemia for five years. Goldish and Aufderheide[35] reported a patient who died of typical bronze diabetes after twenty-two years of refractory anemia. He had received only 1,500 cc. of blood. This is our Case 11, table 1.

It is well established that typical pigmentary cirrhosis and even bronze diabetes may develop in subjects who survive several years of chronic anemia without the help of blood transfusions. The pigment derived from the transfused erythrocytes no doubt intensifies the hemosiderosis of the organs, but it seems highly improbable that it causes the cirrhosis.

Cooley's Anemia. Howell and Wyatt[36] observed massive generalized hemosiderosis and pigmentary cirrhosis in a patient given 225 blood transfusions over a period of thirteen years, and Frumin and associates[37] noted early pigmentary cirrhosis in a patient given 76,655 cc. of blood over a nine-year period. Ellis and associates,[38] in 13 cases of Cooley's anemia transfused over long periods, found 3 cases of severe pigmentary cirrhosis. No cases of diabetes developing in Cooley's anemia have been reported.

An important contribution to the pathogenesis of hemochromatosis was made by Gillman and associates[39] in their study of kwashiorkor in South Africans. Shortly after the infant is weaned and put on an inadequate diet it develops a fatty liver. As the disease continues, the fat disappears and pigment accumulates. Cirrhosis may develop with or without pigmentation, or the liver may be pigmented and noncirrhotic. In about 12.5 per cent of autopsies there was frank pigmentary cirrhosis. The authors believe that cirrhosis and hemosiderosis are independent effects of chronic malnutrition.

Chronic malnutrition probably plays a role in alcoholic cirrhosis, since alcoholics are prone to take an inadequate diet. A majority of chronic alcoholics have fatty noncirrhotic livers, but a large percentage of cirrhotics give a history of alcoholism. In our autopsy series 50 per cent of 633 males and 25 per cent of 299 females admitted excessive consumption of alcohol. The actual incidence of alcoholism is presumably higher, since in many of the clinical records there is no statement concerning the use of alcohol. In subjects with severe portal cirrhosis giving a history of chronic alcoholism the incidence of hemosiderosis of the liver of all degrees was 30 per cent in the males and 18 per cent in the females. The incidence of this disease is therefore the same in alcoholics and nonalcoholics.

The Serum Iron. It is known that the serum iron is much higher than normal in hemochromatosis (Gitlow and Byers,[40] Houston and Thompson,[41] Althausen and his associates,[15] and several other observers report that a subject with hemochromatosis absorbs and retains a much greater proportion of iron given by mouth than does a normal person (Alper and associates,[42] and Peterson[43]). It is also reported that patients with refractory anemia absorb more iron than they use for hemoglobin (Dubach[44]). These observations have led to the view that one of the basic disturbances in hemochromatosis is excessive absorption of iron. A patient with refractory anemia absorbs excessive amounts of iron, which may lead to hemosiderosis even when no blood transfusions are given. The transfusions merely intensify the hemosiderosis.

The cause of the cirrhosis remains obscure. Experimentally, prolonged administration of iron produces intense hemosiderosis but not cirrhosis (Wyatt and Howell,[45] Cappell,[46] Polson[47]). The observations of Gillman and Gillman[48] on pellagra also indicate that the iron deposit is not the cause of the cirrhosis. Cirrhosis and hemochromatosis appear to be independent phenomena caused by some fundamental disturbance.

Vascular Disease in Subjects with Hemochromatosis. Sheldon[11] noted the rarity of atherosclerosis in hemochromatosis, stating that there were only 8 among 311 subjects in which it could have been present. Lawrence[49] commented upon the absence of atherosclerosis in 40 cases of hemochromatosis. In our 11 cases of bronze diabetes (table 2) there was none with a serious vascular lesion. In our 18 cases of diabetic hemochromatosis without melanoderma (table 3) there was one death from coronary thrombosis (No. 28). This subject had grade 1 hemosiderosis of the liver. In the 28 cases of grade 3 hemosiderosis without glycosuria (table 5) there were no serious vascular lesions. There was one death from coronary disease among 57 cases of grade 2 hemosiderosis, and one among 69 cases of grade 1 hemosiderosis. Among 507 cases of nonpigmentary cir-

rhosis there were deaths from vascular disease in 13, and 8 of these patients were diabetics. Of the 15 deaths from vascular disease in the 733 cirrhotics four were due to coronary disease, four to gangrene of the leg, four to primary hypertension with cardiac failure, and three to intracranial hemorrhage.

It is remarkable that diabetics with pigmentary cirrhosis should be free of vascular disease, when over 50 per cent of other diabetics over forty years of age die of some form of it (Bell[50]). Since the incidence of vascular lesions in diabetes increases with the duration of the disease, the shorter duration of diabetes in hemochromatosis may be a factor. However, eight diabetics with nonpigmentary cirrhosis died of vascular lesions after relatively short periods of diabetes.

The very low incidence of death from vascular disease in portal cirrhosis, 15 in 933 cases, or 1.6 per cent, is not surprising, since any lethal disease is associated with a low incidence of other lethal diseases. In the 933 cases of cirrhosis there were only 11 deaths from cancer. These statistics do not mean that alcoholism protects one from coronary disease or cancer, but that it kills before other diseases develop. (As an extreme example, persons killed by automobiles show a very low incidence of coronary disease and cancer.)

The Pancreas in Hemochromatosis. The acinar tissues of the pancreas usually exhibit about the same degree of pigmentation as the liver in bronze diabetes and grade 3 simple hemochromatosis. In grade 2 hemosiderosis of the liver 20 of 28 pancreases were pigmented, and in grade 1 hemosiderosis, 11 of 19. In the lesser degrees of hemosiderosis the pancreas is less frequently pigmented than the liver, but sometimes intense pancreatic pigmentation is associated with grade 1 hemosiderosis of the liver. The pigment is largely confined to the acinar cells but is often present in small amounts in the islets. The pigment in the islets does not produce degranulation of the beta cells or other evidence of injury.

The Islets of Langerhans. In the 11 cases of bronze diabetes (table 1) there were no hyaline islets and the beta cells all showed severe degranulation. In 973 diabetics over fifty years of age there were hyaline islets in 45.7 per cent (Bell[51]), and in 827 diabetics over fifty years of age there was partial to complete degranulation of the beta cells in 35 per cent (Bell[52]). I have been unable to find any reference to the islets in bronze diabetes in the literature. This group of eleven cases is too small to justify any conclusions, but the peculiar islet changes and the absence of vascular disease suggest that bronze diabetes is different from ordinary diabetes. In diabetic hemochromatosis without melanoderma (table 3), 4 of 15 subjects had hyaline islets and 5 of 16 had beta cell degranulation. In group 3 (table 4), hyaline islets without clinical diabetes, 2 of 7 cases had beta cell degranulation, which is strong confirmatory evidence of diabetes.

In group 4 (table 5), grade 3 hemochromatosis without glycosuria, there was no case with hyaline islets, but 6 of 12 had beta cell degranulation, indicating that they were latent diabetics. In groups 5, 6, and 7 there were no hyaline islets and only two subjects had degranulation of the beta cells.

There is no evidence that the diabetes of hemochromatosis is due to injury or destruction of the islets. In routine stains the islets appear entirely normal.

Primary Carcinoma of the Liver. Berk and Lieber[53] found 3 primary carcinomas in 15 cases of hemochromatosis, and Warren and Drake,[54] 6 in 20 cases. The latter authors encountered 24 carcinomas in 127 cases of hemochromatosis. Berk and Lieber[53] found 32 primary carcinomas in 950 cases of cirrhosis (3.5 per cent), and 90 in 1,989 collected cases of cirrhosis (4.5 per cent). In our autopsies there were 35 primary carcinomas of the liver in 633 males (5.5 per cent), and 5 in 299 females (1.7 per cent). In our series primary carcinoma is therefore three times as frequent in males as in females. In the 26 cases in which microscopic sections were available 17 had no hemosiderin in the liver, and 9 had hemosiderosis grades 1 to 3. There were only 4 cases associated with grade 3 hemosiderosis. This is a very small group, but it suggests that primary carcinoma is as frequent in nonpigmentary as in pigmentary cirrhosis, and that it is related to the cirrhosis and not to the pigment.

Discussion. It is evident from the foregoing study that hemochromatosis in the sense of pigmentary cirrhosis is not a sharply defined entity, since there is a gradual blending between fully developed hemochromatosis and ordinary nonpigmented portal cirrhosis. One may restrict the term "hemochromatosis" to livers that contain a large amount of iron, but this is an arbitrary definition. About 34 per cent of males and 23 per cent of females with advanced portal cirrhosis show some degree of hemosiderosis of the liver. We do not know why some of the cirrhotic livers accumulate iron while the majority do not. The siderosis of the liver is not related to the degree of anemia, since the hemoglobin levels average about the same in the pigmented and the nonpigmented. Siderosis of the liver develops less frequently in females than in males and less often progresses to a severe degree. The more severe forms

of pigmentary cirrhosis are much more common in males.

In frank hemochromatosis the serum iron is elevated and there is an increased absorption of iron from the gastrointestinal tract, but the few observations that have been made in ordinary portal cirrhosis indicate a normal iron metabolism. Does an increased absorption of iron convert an ordinary portal cirrhosis into pigmentary cirrhosis? The iron stored in the liver may be utilized in the formation of hemoglobin, since it has been shown that the iron may be removed completely by repeated phlebotomy (Davis and Arrowsmith,[55] Warthin[56]). The immediate cause of siderosis of the liver appears to be excessive absorption and storage of iron, but the basic disturbance is presumably hepatic disease or chronic malnutrition. The studies of Gillman and associates[39] on kwashiorkor indicate that the complete picture of nondiabetic hemochromatosis may be produced by chronic malnutrition. Siderosis is not the cause of the cirrhosis, but when excessive it may cause some functional disturbances.

The relation of diabetes to hemochromatosis is obscure. There is an increased incidence of diabetes in cirrhotic males but not in cirrhotic females. There is a high incidence of diabetes in males with nonpigmentary cirrhosis, indicating that some factor other than hemosiderosis is operative. The number of cases is too few for sound conclusions, but there is a suggestion that diabetes is more frequent in severe pigmentary cirrhosis than in nonpigmentary cirrhosis. The diabetes may be hepatic in origin.

The absence of vascular changes in bronze diabetes indicates a special type of diabetes. The circumstance that none of our eleven cases showed hyaline islets and that all showed severe degranulation of the beta cells supports the view that these are not ordinary cases of diabetes.

It cannot be maintained that the accumulation of hemosiderin in an organ is harmless, since in a few instances massive hemosiderosis of the myocardium has caused cardiac failure. It appears also that subjects with massive hemosiderosis of the liver are more prone to develop diabetes. Possibly the diabetes is hepatic in origin—a result of overloading of the hepatic cells with pigment.

In chronic refractory anemia the increased absorption of iron or failure to utilize it may lead to hemosiderosis, which may be associated with cirrhosis. In rare instances typical bronze diabetes develops. It appears that blood transfusions merely increase the degree of hemosiderosis.

SUMMARY

This study is based on 932 autopsies on subjects with clinical portal cirrhosis. Microscopic sections of the liver were stained for iron in 733 cases.

Some degree of hemosiderosis of the liver was found in 34.2 per cent of 506 males and in 23 per cent of 226 females. The amount of iron varied from a trace to a massive amount. There were all intermediate stages between full-blown hemochromatosis and nonpigmentary cirrhosis. Pigmentary cirrhosis is not a sharply defined entity.

Melanoderma is an infrequent feature of pigmentary cirrhosis.

Diabetes is about five times as frequent in cirrhotic males as in the general autopsy male population, but there is no convincing increase of diabetes in cirrhotic females.

Diabetes may develop in nonpigmentary as well as pigmentary cirrhosis but appears to be more frequent in association with severe hemosiderosis.

There is a very low incidence of atherosclerosis in bronze diabetes as compared with other forms of diabetes.

The absence of hyaline islets and the constant degranulation of the beta cells in bronze diabetes may have some significance.

The more severe degrees of hemosiderosis preponderate in males, but the mild degrees have a nearly equal sex distribution.

A few blood transfusions do not produce hemosiderosis, but repeated transfusions over long periods produce massive hemosiderosis of the viscera. There is no convincing evidence, however, that transfusions cause cirrhosis.

Malignant hepatoma appears to be related to cirrhosis rather than to hemosiderosis of the liver.

SUMMARIO IN INTERLINGUA

Le Relation de Cirrhosis Portal a Hemochromatosis e Diabete Mellite

Le presente studio es basate super 932 autopsias executate in subjectos con clinic cirrhosis portal. Sectiones microscopic del hepate esseva tincturate pro ferro in 733 casos.

Alicun grado de hemosiderosis del hepate esseva incontrate in 34,2 pro cento de 506 masculos e in 23 pro cento de 226 femininas. Le quantitate de ferro variava ab un tracia a un amonta massive. Esseva incontrate omne grados intermediari inter plen hemochromatosis e cirrhosis nonpigmentari. Cirrhosis pigmentari non es un

clarmente definite entitate.

Melanoderma es un infrequente tracto de cirrhosis pigmentari.

Diabete es circa cinque vices plus frequente in masculos cirrhotic que in le autopsiate population mascule in general, sed inter femininas cirrhotic il non ha convincente signos de augmentate diabete.

Diabete pote disveloppar se tanto in nonpigmentari como etiam in pigmentari cirrhosis, sed illo pare esser plus frequente in association con sever hemosiderosis.

Il ha un bassissime frequentia de atherosclerosis in diabete bronzate in comparation con altere formas de diabete.

Le absentia de insulas hyalin e le constante disgranulation de cellulas beta in diabete bronzate pote esser de alicun signification.

Le plus sever grados de hemosiderosis prepondera in masculos, sed le leve casos es quasi equalmente distribuite inter le duo sexos.

Un parve numero de tranfusiones de sanguine non produce hemosiderosis, sed repetite transfusiones in le curso de longe periodos de tempore resulta in massive hemosiderosis del visceres. Del altere latere, il non existe convincente indicios a demonstrar que transfusiones causa cirrhosis.

Maligne hepatoma es apparentemente connectite con cirrhosis plus tosto que con hemosiderosis del hepate.

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DISCUSSION

ARTHUR R. COLWELL, M.D., (*Chicago*): Has Dr. Bell seen any correlation between the degree of cirrhosis and the severity of the hemochromatosis? Second, was there any correlation between the existence of diabetes and the severity of the hemosiderosis in the pancreas?

DR. BELL: In answer to the first question, I have studied only clinical cirrhosis. The amount of iron in the liver bears no relation to the amount of fibrous tissue between the lobules of the liver.

The pancreas shows hemosiderosis almost as frequently as the liver, usually in about the same amounts; but occasionally more intense, occasionally less intense. In some cases with the grade 1 hemosiderosis of the liver, there is a grade 3 hemosiderosis of the pancreas.

HENRY T. RICKETTS, M.D., (*Chicago*): May I reask Dr. Colwell's last question: Is there a correlation between the amount of hemochromatosis of the pancreas and the incidence of diabetes? What is the relation of the pancreatic lesion to the diabetes?

DR. BELL: As I said, I have studied only cirrhotics; when a cirrhotic has diabetes, there is not necessarily any pigment in the pancreas. One-half of the people who have both cirrhosis and diabetes have no pigment in the pancreas or the liver. Cirrhosis with diabetes does not mean hemochromatosis; that is, half of those people have no pigment in either the pancreas or the liver.

J. M. B. BLOODWORTH, JR., M.D., (*Columbus, Ohio*): Dr. Bell, when you mentioned the degranularization of the beta cells, I assume you refer to changes demonstrated by the aldehyde-fuchsin stain.

Obviously, we are dealing with two factors: first, the production; and, second, the release of insulin. There is also no doubt now, I think, that the aldehyde-fuchsin stain does indicate the quantity of insulin within the pancreas.

Do you feel that this staining procedure also gives you a good indication of the activity of the pancreas? In other words, if there are many granulated beta cells, do you feel that production of insulin is high and the opposite true when there are few granulated beta cells?

DR. BELL: I only know the amount which is in the pancreas; I do not know whether it can get out, of course. The amount which is in the pancreas correlates in a general way with the insulin requirement. The young diabetic does not have any; but, if we take the same age group of people, it does not correlate. So I do not know whether that insulin gets out of the pancreas; I have no idea whether it is utilizable.

MARIE ORTMAYER, M.D., (*Chicago*): Dr. Bell, has there been a correlation between the hemosiderin in the stomachs of these patients, as compared with that of the pancreas and liver?

DR. BELL: I do not know. I have not studied the hemosiderin in the stomach. I have noticed it is not in the organs like the adrenal or heart, except in the bronze diabetics; they have it in the heart and sometimes in the adrenals and parathyroids.

Relative Obesity and its Health Significance

Ancel Keys, Ph.D., Minneapolis*

Far more is said and believed about the results of obesity than is actually understood and known. There are emotional and moral connotations to the subject that encourage opinions and hinder analysis. These have their origin in the question of the causes of obesity. Though the present discussion is concerned only with the effect of obesity on health, some preliminary remarks on other matters may help to achieve objectivity in regard to a subject that is seldom critically analyzed.

It is now widely agreed that obesity results simply from overeating and that in the vast majority of cases the overeating cannot be explained or excused on the ground that endocrine or other somatic disturbances make overeating obligatory. This fact reinforces the Calvinist attitude about such matters. We are conditioned from our Puritan forefathers to condemn self-indulgence as a form of immorality, and it would appear that obesity is the bodily expression of such immorality. We are particularly receptive, then, to the idea that obesity is unhealthful because we vaguely feel it is morally wicked. Many persons have some sense of guilt, quite apart from any idea of health, at the end of a particularly hearty meal, and this is reinforced by what they are told by the doctors.

There is no doubt that obesity is objectionable on more than moral grounds. For one thing, it is unsightly and repugnant to the esthetic sense. It makes problems for tailors and dressmakers. It is a physical nuisance to others simply because the obese take up too much space in crowded subways, elevators, and so on. The surgeon, of course, objects to obesity because it obstructs his manipulations. And this leads to the major objection against obesity. Obesity is widely condemned as a general health hazard. Most of the documentation of this is provided by the experience of insurance companies, notably in the important studies of Dublin and Marks[1] of the Metropolitan Life Insurance Company.

The effect of obesity on health and longevity is the basis for a growing campaign for general weight reduction of the American population. Specialists in diabetes readily join the crusade because they know that there is frequently an association between diabetes and obesity and they can point to many patients whose clinical status obviously changes as they change weight. Cardiologists are also in agreement because they know that obesity can impose a serious burden on the diseased heart. The circulation that suffices to cover the energy needs in moving around a mass of 150 pounds may be inadequate to handle a load of 250 pounds. Finally, we can point to the mechanical interference by excess fat in organ functions.

But the purpose of this discussion is not simply to review the indictment against obesity. It may be of greater value, and it is certainly more challenging, to attempt a more detailed analysis of some parts of the problem. First, it is important to make sure that we know exactly what we are talking about when we speak of obesity and overweight. Then we might cast a critical eye, and make a few computations, on the effect of obesity on the total mortality picture. Finally, the specific problem of atherosclerosis may be considered, and this brings up the question of the blood chemistry as related to obesity.

What is Obesity? Obesity means, etymologically, the condition of being overly fat because of overeating. Both in common parlance and in professional discussion this meaning is basic. When it is said that a person is obese, it is generally understood that the person is overly fat and that he got that way by eating too much.

The recognition of obesity is commonly made by simple inspection, and this is satisfactory for some purposes when only extremes in the gradient from emaciation to obesity are concerned. The classification of the great majority of persons in regard to relative obesity is another matter, and any scientific analysis will require a system of measurement. And therein starts the difficulty (Brôzek and Keys,[2] Brôzek,[3] Keys,[4] Keys and Brôzek[5]).

By far the most widely used method of classifying

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people in regard to obesity is to measure the height and weight and refer the finding to a standard table. In this way an expression of relative body weight, as a percentage of "normal" or as pounds of "overweight" or "underweight," is derived. More often than not, this is either explicitly or implicitly translated to mean a corresponding excess or deficit of fat or of adipose tissue; the dietary prescription follows.

Some gross faults in this procedure are obvious, and others appear on closer analysis (Keys and Brôzek[5]). The first objection, of course, is that all weight, whether of fat, muscle, or bone, is considered as equivalent. For the grossly obese or overweight person, who is perhaps fifty or more pounds heavier than the average person of his height, we can be sure that a considerable portion of his excess weight is made up of excess fat. However, it is with such extremes that the need for an exact estimate of obesity is least. The real need for an estimate is when the approximate answer is not evident from simple inspection.

How fat is the man who is 15 per cent overweight according to the tables? On the average, we can say he is rather fat, but careful studies show that some men who are 15 per cent overweight are *very* fat, while the same degree of overweight in some other cases involves *no* excess fat. This means that relative body weight measurements are of very limited value in research as well as in the clinic where individual patients are to be evaluated in regard to actual fatness. However, the body weight is an excellent guide in studying the response of a patient to dietary change.

The necessity for differentiating between overweight and overfatness is important, of course, because the condition of overfatness is metabolically at the opposite pole from that of overweight without overfatness. The latter condition almost invariably means that there is an unusually large muscle mass and a correspondingly high degree of physical activity. The self-selected diet of such a person is not excessive, no matter what the calorie intake and in spite of the height-weight chart. On the other hand, many persons are actually obese though they are not overweight. These are the persons who exercise little and have a subnormal muscle mass but who habitually eat beyond their metabolic needs.

It is useful to consider as illustrations two cases summarized in figure 1. Here are two men of the same age and height. The height-weight table says they should each weigh 70 kg. The average for this age, height, and weight is a body content of about 12 kg. of fat and 30 kg. of muscle. The first man weighs 70 kg.—perfect according to the table—but his body

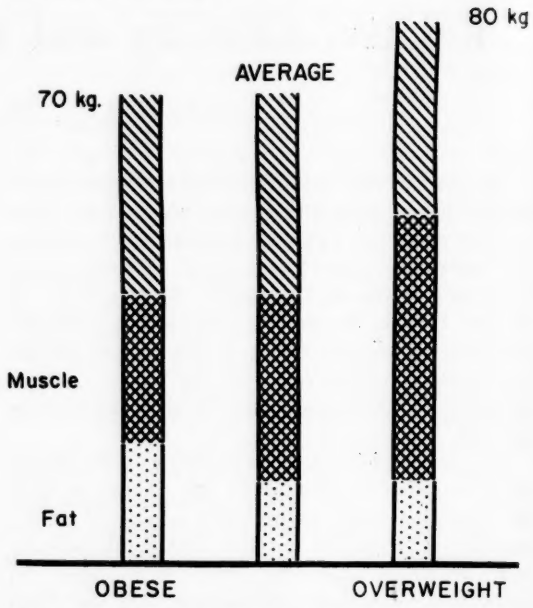

FIG. 1. Schematic comparison of body compositions of three men of identical height, one of whom is obese but not overweight, another being overweight but not obese.

contains 18 kg. of fat and 24 kg. of muscle. He is 50 per cent overfat in spite of the table. The second man weighs 80 kg., but his body contains 12 kg. of fat and 40 kg. of muscle. He is not overfat at all, but the table says he is 15 per cent overweight. If he listens to the advice of a physician he is apt to go on a diet, making himself and his wife unhappy, and if he persists he must go into negative nitrogen balance to satisfy the physician.

The Composition of the Body. The composition of the body is the key to these questions. It is still difficult to make an exact estimate of the body without spoiling the body for further use, but some indirect methods of analysis are now being developed and useful estimates are not too difficult to get.

The body may be subdivided in several ways according to the purpose in mind and the methods available. In regard to obesity, and for most questions of metabolism, the body may be considered to consist of fat, comprising from about 2 per cent to as much as 50 per cent of the total weight, and the nonfatty remainder. But of this nonfatty remainder only a part is metabolically active. The bone mineral and the extracellular fluid are appreciable masses, but they do not consume or demand appreciable amounts of metabolic energy. The "active" tissue or "cell" mass of the body, then,

is estimated by subtracting from the gross weight the fat, bone mineral, and extracellular fluid. In the normal young man of average fatness slightly less than two-thirds of the body weight is "active" tissue.

Estimation of Body Fat. Keys and Brôzek[5] have recently reviewed the whole subject of the composition of the body and its estimation by indirect methods applicable to living persons. Here only a few points may be noted. The indirect methods take advantage of the facts that the gross composition of the active metabolizing cells of the body is remarkably constant and that bone mineral is only a relatively small part of the total body mass, never as much as 10 per cent and usually nearer 5 per cent.

The most variable component of the body mass is fat. Body fat has the useful peculiarity that it is considerably less dense than the rest of the body. A cubic centimeter of pure human fat (ether extract) weighs only about 0.9 gm. at body temperature (37° C.), whereas the density of the rest of the body is more like 1.1 gm. per cubic centimeter. A measurement of the density of the whole body, then, should provide a means for estimating the proportions of fat and of nonfat in it.

The simplest approximation is to consider the body to consist of fat, with density α, and nonfat, with density β. If the density of the whole body is D, and the relative masses of fat and of nonfat in the body are X and Y, respectively, then we may write:

$$D = \frac{X + Y}{(X/\alpha) + (Y/\beta)}$$

Hence it appears that if we know the average densities of fat and of nonfat in human bodies, a simple measurement of gross body density will at once show the proportion of fat.

Unfortunately, the matter is a little more complicated than this. We can measure the body density by weighing it both in air and under water, but we must then correct the apparent volume for the air in the lungs. And we have found that it does not suffice merely to subtract some standard value for residual air; this residual air is so variable in amount from person to person, and even in the same person, that only a very crude estimate can be made in this way.

We have now learned how to measure the residual air at the moment the body weight is recorded under water. This, however, makes the method too complicated for all but some research applications. We can also get around the problem of residual air by measuring the body volume in a gas chamber, but this is even more complicated. And, in any case, there are other questions to consider.

The largest mass in the body is water. In the cells, water is a fairly constant proportion, and the extracellular fluid likewise is fairly constant in healthy persons. But in disease and in different physiologic states the body water varies so much that it changes the density of the whole body. Hence to be safe, particularly in patients, it is desirable to measure the body water as well as the gross body density in order to get a reliable measure of body fat. This can be done, of course, by applying the dilution principle and determining the volume in which a given water indicator is distributed. Heavy water may be used for this purpose. Antipyrine and urea have also been used, although we despair of antipyrine after four years of trial.

The estimation of body fatness simply from an estimation of total body water, without measuring body density, has been advocated. This method can yield useful results in strictly normal persons, but it is hopelessly bad in the presence of even slight alterations in hydration. And it must be remarked that the measurement of total body water is not the simplest procedure in the world. We find it much easier to measure body density.

We may hope that the methods for measuring body density and total body water will some day be greatly simplified, but there is no prospect that such methods will soon become suitable for use in the office or at the bedside. Fortunately, there is another way of estimating body fatness which seems to hold much promise for many applications.

Something like half of the body fat in man is subcutaneous, and that is accessible to semidirect measurement. A soft-tissue roentgenogram of the edge of the body or of an extremity shows the subcutaneous fat layer quite nicely, but to get a good estimate of subcutaneous fatness in this way requires a series of films with careful positioning. For many purposes the same information may be obtained far more simply with skinfold calipers.

The idea of estimating fatness by pinching up a fold of the skin with its attached subcutaneous fat is very old. It was probably used by the earliest animal traders as well as by those in the market for wives. Skinfold calipers have been used sporadically for over thirty years, but neither the method nor the data have been standardized. There are two problems. First, the subcutaneous fat layer is not uniform all over the body and the distribution varies with age and sex. This

means that more than one site of measurement must be used. The two most assessible and informative sites are over the triceps muscle of the upper arm and over the tip of the scapula. Second, the skinfold is compressible, and the pressure under which the measurement is made must be standardized. A pressure of 10 gm. per square millimeter of caliper jaw face seems to be optimal.

Prediction equations for estimating body density, and hence total body fat, from skinfolds can be developed (Brôzek and Keys[6]), but it may be simpler to develop a scale of fatness directly from skinfold measurements. A man whose triceps skinfold measures 5 mm. (double thickness) is very thin, and a value of 25 mm. at this site means that he is very fat, regardless of what his gross weight may be. These are not the extremes of measurement, but they illustrate the point that the skinfold may easily be four or five times thicker in a fat man than in a lean one. Differences in fatness show up most clearly when we measure fat itself. Note that true skin is rather less than 2 mm. of the fold thickness.

Figure 2 shows the relationship of subcutaneous fat thickness to relative body weight in a random sample of clinically healthy men. The "subcutaneous fat" indicated here is one-fourth the sum of the thickness of the skinfolds over the triceps and over the tip of the scapula; in other words, it is a rough average for the single thickness. There is a high but far from perfect correlation between these two measures in this sample, in which relative body weights range from —30 to +45 per cent.

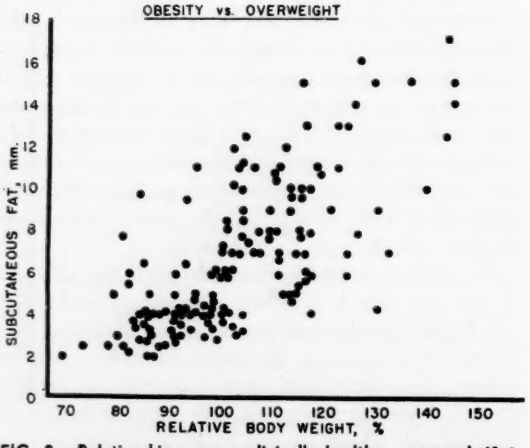

FIG. 2. Relationship, among clinically healthy men aged 40 to 50, between relative body weight (as per cent of United States average for equal height and age) and body fatness.

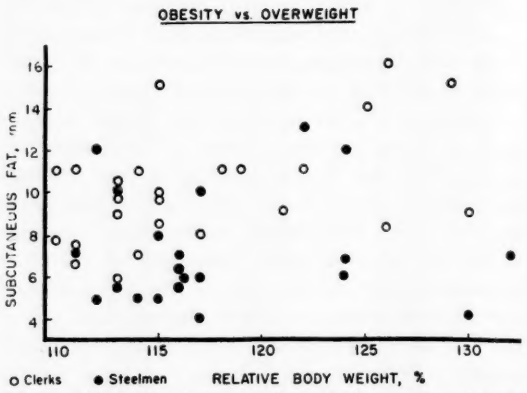

FIG. 3. Relationship between relative body weight and body fatness among clinically healthy middle-aged men who are overweight according to the usual United States height-weight tables.

But, as shown in figure 3, when attention is concentrated on men in the overweight class, from +10 to +34 per cent overweight, there is almost no correlation between the degree of overweight and the degree of subcutaneous fatness. This figure also shows another important point. The measurements given here were made on two different groups of men. The sedentary clerical workers clearly tend to be fatter in proportion to their weight than do the employees in the steel mill. This is reasonable, of course, but it emphasizes the fallacy of using a simple body weight scale in which this difference would remain hidden.

Overweight and Mortality. With a better comprehension of the gross composition of the body and the complexity of what is grouped together in the gross body weight, it is unsatisfying to discuss the health significance of overweight without further specification. But data obtained with better measures are still very scarce, and it is useful to look critically at the thesis, currently being advocated, that overweight is the major health problem of America today.

As noted earlier, the most impressive evidence for this thesis is provided by the experience of the life insurance companies.[1] In general, these companies have kept special record of, and charge extra premiums to, their policy holders who are as much as 20 per cent or more heavier than the average policy holder of the same age and weight. These are the overweight persons, frequently identified as the obese, whose mortality records are the basis for most of the shouting. Roughly, the mortality of these overweights runs around 50 per cent higher than that of the rest of the policy holders for the first twenty years or so after issue of their insurance policies.

These "overweights" are rather peculiar. They comprise only a very small percentage of the policy holders (as few as 2 per cent or less in some companies), though it has been claimed that persons of that degree of overweight comprise 7 per cent or more of the general population (Armstrong and others[7]). Hence it seems that overweights are not fully represented in the insured population, and hence it is very questionable whether those who *are* insured are actually representative of all overweight people. Why are these particular overweight persons so anxious to get life insurance that they pay special premiums for it when, apparently, most overweight persons will not do this?

There is in this connection a significant example to cite from the relatively recent history of the insurance business. For a long time almost all life insurance policies were held by men; it was not customary for women to apply for or to take out insurance policies on their lives. Fifty years ago, when few women carried life insurance, they paid higher premiums than men, and the mortality experience of the life insurance companies indicated women to be poorer risks than men, though in the total population, noninsured and insured, the women had no such adverse mortality. When competitive developments in the life insurance industry produced lower premiums for women and brought greater numbers of them into the policy-holder group, the adverse mortality experience with women promptly disappeared. It was clear that the few women who previously had been willing to pay high premiums for insurance were not representative of women in general but were, on the average, considerably less favorable life risks. Somehow, those women most likely to die prematurely were those most likely to take out life insurance in spite of high premiums.

It is reasonable to suggest that the situation with regard to overweight may be somewhat analogous. I have no doubt that the life expectancy of grossly overweight men, insured or not, is less than that of men of ordinary weight for height. But it is highly probable that the experience of the life insurance companies, drawn from a peculiar sample of overweight persons, may exaggerate the actual difference.

However, let us accept for the moment the questionable hypothesis that insured persons who pay extra premiums because of overweight are truly representative of all persons who are equally overweight. The published life insurance data are exasperating when it is desired to construct a proper table of mortality rates at given age, but the most recent figures indicate roughly 50 per cent excess mortality among those men who are so overweight (20 to 74 per cent above standard average weight for height and age) that they pay special premiums.

The question then is, what would be the effect on national mortality rates at different ages if all men of this degree of overweight were removed from the vital statistics? In other words, what would be the average mortality rate if we had no overweight problem in the United States? There are no reliable figures as to the frequency of overweight in the population, but it has been suggested that as many as 10 per cent may be in the overweight class corresponding to the extra-premium payers. It is possible, on this basis, to calculate a table of vital statistics for the remaining 90 per cent. If Y is the observed mortality rate at given age and if X is the rate that would be found in the population when the overweights are removed, then

$$0.9\,X + 1.5\,(0.1\,X) = Y$$

and X turns out to be 95.2 per cent of Y. The mortality rate at ages thirty to seventy would decline by 4.8 per cent. This is a maximum estimate.

For several years I have been pointing out the singularly disquieting fact that over much of the span of adult life American men have high mortality rates in comparison with men in many other countries. A frequent comment I receive is that our poor mortality record shows the great need to correct our high incidence of overweight and/or obesity. And it is implied that if we corrected our overweight, then we should assume our rightful place at the head of the list of countries in health. Unfortunately, as figures 4 and 5 show, more than the correction of overweight is needed to give our men from the thirties to age seventy a good mortality record. In these figures comparison is made with Sweden and with Italy, primarily because I have research interests in these countries, but other countries would show the point as well—Norway, the Netherlands, England and Wales, and so on.

A second point in this comparison should be observed. In most of these countries with superior adult mortality rates we have no reason to believe that the incidence of obesity is any less than in the United States. We have studied a number of samples of men in Italy, for example, and find that their relative body weight and the frequency of overweight are much the same as in the United States.

Now, these comparisons of mortality rates have been made for deaths from all causes. We have a very high death rate from violence, not only in automobile accidents but also from suicide, especially from "bromacide" [a murder through the use of (wrong) food].

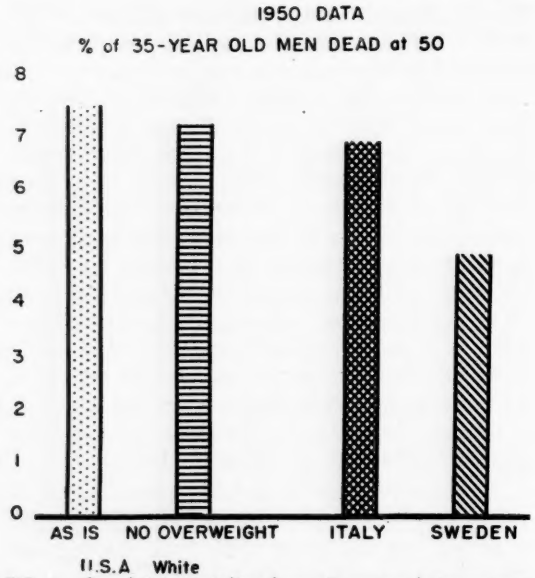

FIG. 4. Cumulative mortality, from all causes, between ages 35 and 50 of United States white men and men in Italy and Sweden, together with the estimated mortality for United States white men excluding 10 per cent of these men who may correspond in obesity and mortality experience to life insurance estimates.

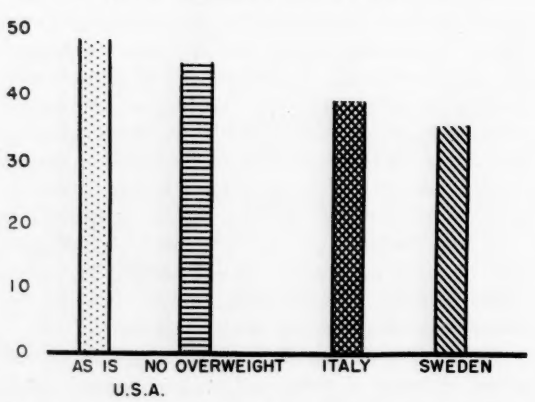

FIG. 5. Cumulative mortality, as in figure 4, between ages 35 and 70.

Around 8,000 persons are murdered here each year; the figures for Italy and Sweden, adjusted to our total population, are roughly 2,400 and 1,000, respectively. But our excessive mortality among adult males up to age seventy, at least, remains after correction for all deaths from violence.

Systematic study of vital statistics shows, in fact, that one cause of death alone more than accounts for the poor over-all mortality of American men. That is coronary heart disease. Coronary heart disease is now credited with being responsible for about one-third of all deaths among United States white men between the ages of thirty and seventy. This immediately raises the question as to the relationship between overweight and/or obesity on the one hand and coronary heart disease on the other.

It is widely believed that coronary heart disease is a special threat to the overweight man, but it seems to be remarkably difficult to prove this. The life insurance data offer some evidence, but as published they are not statistically very convincing. And when we turn to other sources of evidence the supposed predilection of coronary heart disease for overweight persons largely disappears (Keys[8]).

An obvious method of examining this question is to seek out hospital patients who have just had myocardial infarctions and to check their heights and weights. One of the best series, summarized in table 1, is that of Billings and colleagues[9] at Nashville, Tennessee, who provided such data for 240 infarctions. These fail to show any peculiarity in their relative weight distribution as compared with the general population. The most interesting features in their data are, first, an indication that underweight is unduly frequent among those patients who die of myocardial infarction in the first thirty days; and, second, the indication that a fatal outcome of infarction is less frequent among overweight persons than among persons of normal relative weight.

TABLE 1

Incidence of overweight and underweight among 240 patients with acute myocardial infarction as reported by Billings, Kalstone, and Spencer[9] compared with the incidence among the general population as estimated in the Proceedings of the Life Extension Examiners (*1*:89, 1939). "Fatal" refers to those patients who died within thirty days.

Weight group	General population	Myocardial infarction		
		All	Fatal	Survivors
Over	28	33	27	37
Normal	59	51	49	51
Under	13	16	24	12
	100	100	100	100

The best series of young coronary patients is that carefully studied by Garn, Gertler, Levine, and White.[10] Their findings are summarized in figure 6. Their pa-

tients tended to be overweight according to United States Army standards for inductees, but so did their healthy controls. It is clear that the distribution of relative body weights in their 97 men under forty years of age who had infarcts is identical with that among men of the same age in the same occupation.

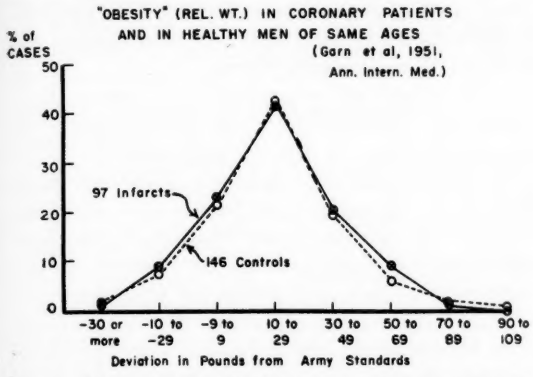

FIG. 6. Relative body weight (as deviation from United States Army inductees) distribution among men under 40 years of age.

A most significant series for these questions is that of Yater and his associates[11] on 866 fatal cases of coronary heart disease, with necropsy in 450, among United States Army personnel under forty years of age. From a preliminary examination of the data in eighty of these cases, French and Dock[12] reported a tendency for these soldiers to be overweight (figure 7). The raw data for the full series, as given by Yater and co-workers and shown in figure 8, exhibit the trend they saw. Their conclusion that overweight is an important etiologic factor in coronary heart disease was widely accepted, but on closer study the picture is quite different, as is evident in figure 8.

The body weight distribution used by French and Dock as the "normal" is that of men at the time of induction into the Army. Almost all of the inductees were in the low twenties, of course, and almost all of them promptly gained weight after getting into the Army. At time of death the men who had infarctions averaged more than ten years older, and they, like their healthy fellows, naturally tended to be considerably heavier than the youngsters just entering the service. An excellent control series was provided by the men of the same age who were killed in military accidents in this same period. The relative weight distribution is substantially identical.

Our own experience in Minnesota with men from forty to sixty-five years of age is in full agreement.

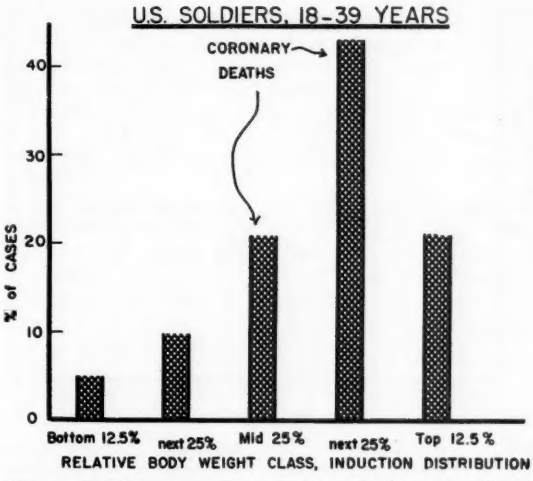

FIG. 7. Distribution of relative body weight among 80 United States soldiers who died of coronary heart disease at less than 40 years of age. The relative body weight classes are those for all men at the time of induction into the Army. Data from French and Dock, 1944.

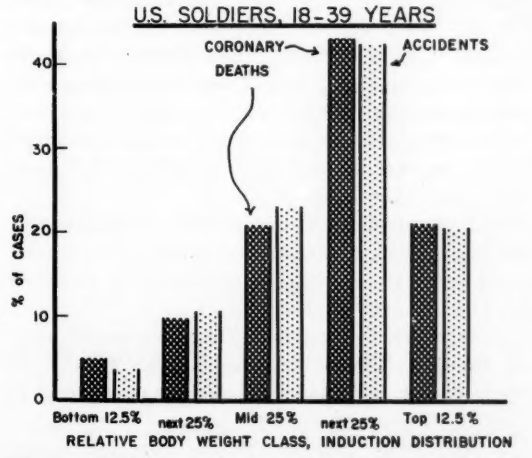

FIG. 8. Distribution of relative body weight among 866 United States soldiers who died of coronary heart disease at less than 40 years of age, together with the data on United States soldiers of the same age killed in military accidents during the same period. Data from Yater and co-workers (1948).

Twenty-six per cent of the men with coronary heart disease are 10 per cent or more overweight; this is close to the expectation among clinically healthy men. The distribution of the relative body weights of these patients is shown in figure 9.

This is the way the evidence adds up. It is entirely conceivable that if there were comparable data on actual obesity—that is, on fatness—the picture might be dif-

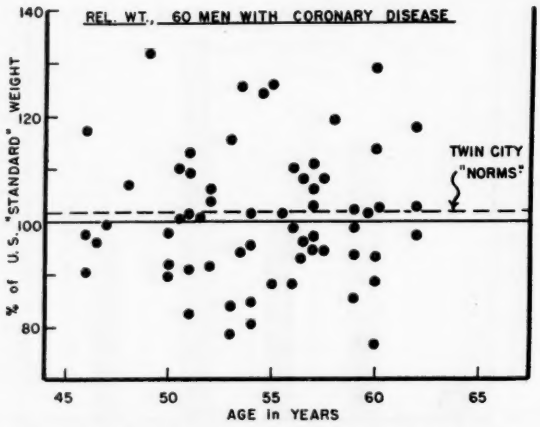

FIG. 9. Relative body weights, as percentages of United States averages for given heights and ages, for sixty men with clear clinical evidence of clinical heart disease.

ferent. But such data remain to be collected. In our own studies at Minnesota the material on body fatness in coronary disease is still too small to discuss as yet. We have been much more concerned with the question of fats, or rather cholesterol and lipoproteins in the blood, but that would require another and longer address for adequate treatment.

Now, what is the upshot of the present discussion? There is no intention to defend obesity here. The points I have tried to make are as follows:

1. It is essential to discriminate between obesity and overweight. These two characteristics are well correlated at the extremes, poorly correlated where it counts in the range of most of the population.

2. Metabolically, the condition of overweight without obesity is diametrically opposed to the condition of simply obesity, and the relationships to disease may be expected to be quite different.

3. The belief that an effective campaign against overweight would have large effects on the public health picture in the United States is not justifiable on the evidence available.

4. The adult American male, as compared with men of the same age in many other countries, has a very poor total mortality record. There seems to be no possibility that this adverse status would be greatly changed by the elimination of overweight.

5. Coronary heart disease is the outstanding cause of death among American men today, and an excessive incidence of this disease in the United States fully accounts for our unfavorable health record in comparison to many other countries.

6. The bulk of the evidence is opposed to the common belief that overweight is an important factor in the development of coronary heart disease or the production of myocardial infarction.

7. Finally, it is abundantly clear that we need a great deal more research on the effects of obesity versus those of overweight, and on the characteristics of populations and how they live, in relation to the incidence of disease among them.

SUMMARIO IN INTERLINGUA

Obesitate Relative e Su Signification Sanitari

1. Il es del prime importantia discriminar inter obesitate e excesso de peso. Iste duo characteristicas es ben correlationate al extremitates, sed illos monstra un magre correlation in le importantissime areas intermediari que comprende le plus grande portion del population.

2. Ab le puncto de vista metabolic le condition de excesso de peso sin obesitate es diametralmente opponite al condition de simple obesitate, e il non es a supponer que le relation a statos pathologic debe esser simile in ambe casos.

3. Le datos nunc disponibile non justifica le expectation que un campania efficace contra excessos de peso influerea significativemente super le stato de valetude public in le Statos Unite.

4. Le masculo median del Statos Unite ha un pauco favorabile statistica de mortalitate in comparation con masculos del mesme etate in multe altere paises. Il pare impossibile que iste stato negative cambiarea grandemente per le elimination de excessos de peso.

5. Morbo cardiac coronari es hodie le prominente causa de morte in masculos statounitese. Le excessive frequentia de iste morbo in le Statos Unite explica le disfavorabile statistica de valetude in nostre pais in comparation con multe altere paises.

6. Le major portion del datos accumulate contradice le currente opinion que excesso de peso es un factor importante in le disveloppamento de morbo cardiac coronari o in le production de infarcimento myocardial.

7. In conclusion, il es abundantemente clar que nos require ancora multe recercas in re le effectos comparative de obesitate e de excesso de peso e in re le characteristicas e formas de vita de varie populationes in relation a lor statisticas pathologic.

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The Nutritional Resources of the World

There is ample justification for concern about adequate food supplies for future generations of mankind, but this concern should be broadened to include the immediate problem of an adequate standard of living for the world's present population. The successful solution of the immediate problems would furnish the best background of experience for meeting those that will arise in the future. First steps include the acceptance by society of responsibilities for the extension of the benefits of education throughout the world and provision for the type of scientific, economic, social, political, and religious leadership necessary to assure food for all on a continuing basis.

Striking improvements in the food supply can be readily made through the application of present knowledge, if the foregoing conditions are met. The rapid pace of modern science, both pure and applied, gives promise that future benefits may be much greater than those thus far experienced. Current advances do not signal the end of a technical road but rather that the great scientific developments still lie ahead. If we have the intelligence and wisdom to recognize human responsibilities and to make constructive use of our natural and human resources, we can look forward to a better world in the future and improved standards of living for all.

From "Food for the Future" by J. G. Harrar, *Science* *122*:313-16, Aug. 19, 1955.

The Coefficient of Digestibility

The word "digestibility" has been given several meanings: (1) the percentages of the several nutrients of a food which are available to the body for use as fuel or building material—the "coefficient of digestibility"; (2) the ease and comfort with which it is assimilated, as measured by the demands it makes upon the stomach and intestines; (3) the smallness of the residue which it leaves in the intestines; and (4) the infrequency with which it calls forth untoward symptoms. It is used in the first sense in scientific literature and with the other meanings in medical practice and everyday parlance.

The coefficient of digestibility of all foods is surprisingly large. Atwater showed that of the nutrients contained in a mixed diet, the following average amounts are utilized: protein, 92 per cent; fat, 95 per cent; and carbohydrate, 97 per cent.

Foodstuffs from animal sources are more completely utilized than those from vegetables. Hegsted and his associates found the "digestibility value" of the protein in an all-vegetable diet to be 87.7 per cent. Diets containing meat and bread showed slightly higher values, and those containing soy flour and wheat germ slightly lower values. Of protein from animals, 97 per cent is used; of protein from vegetables, 84 per cent; of fat from animals, 95 per cent; of fat from vegetables, 90 per cent; of carbohydrate from animals, 98 per cent; and of carbohydrate from vegetables, 97 per cent.

From the book *Nutrition and Diet in Health and Disease* by James S. McLester, M.D., and William J. Darby, M.D., Ph.D. Philadelphia, W. B. Saunders Co., 1952, 6th ed., p. 135.

The Course and Complications of Diabetes Mellitus

Data in 331 Cases observed regularly in a Diabetic Clinic

Elaine P. Ralli, M.D., Elisabeth Street, B.A.,†*
and Sidney Pell, M.A.,‡ New York

It has become increasingly evident that diabetes mellitus involves much more than a simple disturbance in carbohydrate metabolism. Observations of patients with this disease by many investigators indicate that a significant number of them develop degenerative lesions of the arteries at an earlier age than do nondiabetics.[1-4] Furthermore, in a large diabetic clinic where patients are observed over periods of years, it is equally obvious that the diabetic patient is liable to the same diseases as are nondiabetics. With the increased survival of the diabetic patient, which has resulted largely from the use of insulin and proper diet, the opportunities for observing the complications that occur with this disease have increased.

The Diabetic Clinics of the Third (New York University) Medical Division of Bellevue Hospital were established in 1928. A significant number of the patients attending this clinic have been coming for many years and, preparatory to an investigation of the factors contributing to the degenerative lesions, an analysis has been made of the status of a portion of the patients attending these clinics.

PRESENT STUDY

The first part of this report consists of an analysis of 331 cases. The data on all patients attending the Clinics from November 1950 to April 1951 are included. Of these, 126 were males and 205 were females. The ages ranged from 5 to over 70 years. Seventeen per cent were in the age group from 20 through 49 years. Eighty-one per cent were in the age group from 50 to over 70 years.

In table 1, the age in each sex group is reported. During the period of the study a greater number of female than of male patients with diabetes were seen, and it is obvious that more female than male patients with diabetes are attending the clinic. Actually, it is elderly females who form the greatest proportion of the total number (32 per cent).

TABLE 1
Age and sex of patients

	Total		Male		Female	
Age in Years	No.	Per cent	No.	Per cent	No.	Per cent
	331	100	126	38	205	62
29 or less	17	5	10	3	7	2
30-39	13	4	4	1	9	3
40-49	32	9	8	2	24	7
50-59	89	27	30	9	59	18
60-69	118	36	45	14	73	22
70 and over	62	19	29	9	33	10

In table 2 are shown the age at onset and the duration of the diabetes. The onset increased after 40 years of age and in our group of patients reached its peak at 50 to 59 years of age. The effect of insulin in prolonging the life of the patient is shown by the duration of the disease, which had existed for 20 years or longer in 15 per cent of the patients.

TABLE 2
Age of onset and duration of diabetes

	Number	Per cent
Age at onset of diabetes		
9 yrs. or less	7	2
10-19	11	3
20-29	20	6
30-39	28	8
40-49	88	27
50-59	96	29
60-69	63	19
70 and over	12	4
No data	6	2
Duration of diabetes		
4 yrs. or less	98	29
5-9	76	23
10-14	62	19
15-19	46	14
20-24	34	10
25-29	6	2
30-34	3	1
No data	6	2

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As shown in table 3, of the 331 patients, 98 did not require insulin to control the glycosuria. Two hundred and thirty-three of the patients (70 per cent) required insulin. The types of insulin used were regular, crystalline, protamine zinc, or a combination of these. At the time that this study was made, the number of patients taking NPH insulin was small and this insulin had been used for a relatively short period of time. We therefore did not include any data on NPH insulin.

TABLE 3
Daily injections of insulin taken by patient, types of insulin and number of injections daily

	Number	Per cent
Units of insulin taken daily		
None	98	30
5-14	43	13
15-29	76	23
30 or more	114	34
Type of insulin taken		
None	98	30
Regular or crystalline	124	37
Protamine zinc	47	14
Combinations	62	19
Number of injections daily		
None	98	30
1	90	27
2	113	34
3	26	8
4	4	1

The amount and types of insulin required by the patients taking insulin are reported in table 4. Fifty-three per cent of the group requiring insulin took either regular or crystalline insulin only, 20 per cent took protamine zinc only, and 27 per cent were treated with a combination of protamine zinc and quick-acting insulin. One hundred and fourteen (49 per cent) of the patients taking insulin required 30 or more units daily. It was observed that combinations of protamine zinc and quick-acting insulin were used more frequently to control the glycosuria in those patients requiring 30 or more units of insulin daily.

To obtain an indication of the severity of the diabetes, an arbitrary distinction of severity based on the amount of insulin taken daily was used. Patients taking no insulin were classified as mild, those taking from 5 to 15 units daily as moderate, those taking from 15 to 30 units as moderately severe, and those taking more than 30 units as severe. Obviously there could be considerable discussion as to such a classification, but it has served as a basis for evaluating the severity of the diabetes. In table 5, the relation of the severity of the diabetes to the age of onset is given. On the basis of this classification, 30 per cent of the patients were mild diabetics, 13 per

TABLE 4
Daily units of insulin by type of insulin

Units of insulin daily	Total number of patients taking insulin		Regular or crystalline insulin only		Protamine zinc insulin only		Combinations of protamine zinc and regular insulin	
	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent
	233	100	124	100	47	100	62	100
5-14	43	18	28	23	14	30	1	2
15-29	76	33	37	30	25	53	14	22
30 or more	114	49	59	47	8	17	47	76

TABLE 5
Relation of present severity of diabetes to age at onset

Onset at	Total number of patients		Mild		Moderate		Moderate-Severe		Severe	
	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent
	331	100	98	100	43	100	76	100	114	100
9 yrs. or less	7	2	0	0	0	0	0	0	7	6
10-19	11	3	0	0	0	0	1	1	10	9
20-29	20	6	2	2	1	2	3	4	14	12
30-39	28	8	5	5	3	7	3	4	17	15
40-49	88	27	18	18	12	28	28	37	30	26
50-59	96	29	38	39	16	37	22	29	20	17
60-69	63	19	26	27	9	21	17	22	11	10
70 and over	12	4	8	8	0	0	0	0	4	4
No data	6	2	1	1	2	5	2	3	1	1

Note: The purpose of this analysis was to see if there is any relation between the severity of diabetes, as measured by the insulin requirement, and the age of onset of the diabetes. The following criteria were used to classify patients as mild, moderate, moderate-severe, or severe diabetics:

Mild — Taking no insulin
Moderate — Taking 5 to 14 units daily
Moderate-Severe — Taking 15 to 29 units daily
Severe — Taking 30 or more units daily

cent moderate, 23 per cent moderately severe, and 34 per cent severe. The mild group were patients in whom the onset usually occurred over the age of 40 years. A small number of patients developed a mild form of diabetes between 20 and 39 years of age.

Further examination of this table reveals that the more severe diabetics usually developed their diabetes before 49 years of age. However, 32 per cent of the severe diabetics became diabetic after the age of 49. In a small group of patients in whom the onset of the diabetes occurred at 70 years or more, fairly large doses of insulin were required to control the glycosuria.

In table 6 the severity of the disease in relation to the present age of the patient is given. This table represents the age distribution and the severity of the diabetes at the time the study was made. Probably because the disease had had its inception at an earlier age, we find a significant number of patients requiring large doses of insulin in the age group of 49 or more years. As shown in table 7, allowing for the present age of the patient, there was a negative correlation between the severity of diabetes indicated by the daily insulin requirement and the age of onset. A second partial correlation between the present age of the patient and the severity of the diabetes, holding age of onset constant, showed no significant relationship.

From these 331 diabetic patients, 194 who had attended the clinic for 5 years or more were studied in greater detail. These data were collected from October 1951 to April 1952, as the patients visited the clinic. The complications present and their effect on insulin requirements and the course of the disease were analyzed.

Frequency distributions of age, sex, age at onset, and duration of diabetes showed the 194 patients to be very similar to the larger group of 331 patients in regard to these characteristics. In this group of 104 patients, 63 per cent were females, 37 per cent were males. Ninety per cent were Caucasian and the remainder non-Caucasian. The ages ranged from 8 to 80 years. Ninety-three per cent of the patients were over the age of 40.

The age of onset of the diabetes ranged from 2 to 70 years of age. The greater percentage of the patients had developed their diabetes between the ages of 40 and 59 years (64 per cent). The duration of the diabetes varied from 5 to more than 33 years, but in the bulk of the patients (94 per cent) the duration was from 5 to 25 years. The greatest number of patients had attended the clinic for 5 to 8 years, but 21 per cent had attended it for 17 years or more. During the period that these 194 patients had been attending the clinic 62, or 32 per cent, had never required hospitalization. This, we believe, points up the importance of ambulatory care in the management of the patient. With the increased cost

TABLE 7
Correlation coefficients

The following correlation coefficients measure relationships between two or more of the following variables:
Present daily insulin dose
Age at onset of diabetes
Duration of diabetes (in years)

	Coefficient of correlation	
	Linear	Partial
*Present daily insulin dose—age at onset of diabetes	—.47	
Present daily insulin dose—duration of diabetes	.20	
*Present daily insulin dose—age at onset of diabetes, after removing the effect of duration		—.44
Present daily insulin dose—duration of diabetes, after removing the effect of age at onset		.04

*Significantly different from zero at the .05 level of significance.

TABLE 6
Relation of severity of diabetes to present age of patient

Present age	Total number of patients		Mild		Moderate		Moderate-Severe		Severe	
	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent
	331	100	98	100	43	100	76	100	114	100
9 yrs. or less	2	1	0	0	0	0	0	0	2	2
10-19	4	1	0	0	0	0	0	0	4	3
20-29	11	3	1	1	0	0	1	1	9	8
30-39	13	4	3	3	0	0	1	1	9	8
40-49	32	10	5	5	2	5	8	11	17	15
50-59	89	27	27	28	16	37	18	24	28	25
60-69	118	35	36	37	15	35	36	47	31	27
70-79	56	17	23	23	10	23	10	13	13	11
80 and over	6	2	3	3	0	0	2	3	1	1

Note: The following criteria were used to classify patients as mild, moderate, moderate-severe, or severe diabetics:

Mild — Taking no insulin
Moderate — Taking 5 to 14 units daily
Moderate-Severe — Taking 15 to 29 units daily
Severe — Taking 30 or more units daily

of hospitalization, both to the patient and to hospitals, it is apparent that care of the patient which obviates hospitalization is of real importance. Twenty-three per cent of the patients had had one hospital admission, 18 per cent two, and 9 per cent three. A small number of patients had required four or more admissions to the hospital. Among this group were patients who were always careless about the control of their diabetes. This was often the result of a poor home environment.

The severity of the diabetes, as judged by the amount of insulin taken daily, is given in table 8. Twenty per cent of the patients required no insulin and 12 per cent only required up to 14 units daily. These two groups would constitute the mild to moderately severe diabetics. Twenty-three per cent required from 15 to 29 units daily, 45 per cent required 30 or more units daily. Twenty-five per cent of all of the patients required more than 45 units of insulin daily.

TABLE 8
Units of insulin taken daily

Units of insulin	Number	Per cent
None	40	20
5-14	23	12
15-29	44	23
30 or more	87	45

Diabetes has been considered for years a hereditary disease. In table 9 the family history of diabetes in relation to the age at onset is reported. In 42 cases there was a family history of diabetes. Of patients with no family history of the disease, 47 per cent developed the disease at 50 years of age or more. Of patients with a family history of diabetes, 22 per cent developed the disease at 50 years of age or more. From an etiologic point of view, this suggests that certain factors associated with aging may be responsible for the disturbance in carbohydrate metabolism. In the patients with a family history of diabetes, a greater percentage developed the disease before the age of 50. The mean age of onset of the group with the family history was 41 years and the mean age of onset of the group without a family history was 46 years. A Fisher "t" test indicates that these means are significantly different.

To explore this question further, the present severity of the diabetes was studied in relation to the family history of diabetes (table 10). Using the same classifica-

TABLE 9
Family history of diabetes and age at onset of diabetes

Onset at	No. of Patients		With family history		Without family history	
	Total	Per cent	No.	Per cent	No.	Per cent
	194	100	42	100	152	100
9'yrs. or less	5	2	3	7	2	1
10-19	9	5	1	2	8	5
20-29	10	5	1	2	9	6
30-39	25	13	10	24	15	10
40-49	65	33	18	43	47	31
50-59	60	31	6	15	54	35
60-69	18	9	3	7	15	10
70 and over	1	1	0	0	1	1
Unknown	1	1	0	0	1	1
Mean			41		46	
Standard deviation			14		13	

Note: Fisher's "t" test indicates that the mean age at onset of diabetes of patients without a family history of diabetes is significantly greater than the mean age at onset of diabetes of patients with a family history of diabetes.

TABLE 10
Family history of diabetes and present severity of diabetes

Present severity of diabetes	No. of patients		With family history		Without family history	
	Total	Per cent	No.	Per cent (22)	No.	Per cent (78)
	194	100	42	100	152	100
Mild	40	20	11	26	29	19
Moderate	23	12	7	17	16	11
Moderate-Severe	44	23	4	9	40	26
Severe	87	45	20	48	67	44

	Mean	Standard deviation
Daily units of insulin taken by patients with family history of diabetes	27	24
Daily units of insulin taken by patients without family history of diabetes	30	29

Note: Fisher's "t" test shows no evidence that the mean daily insulin dosage of patients without a family history of diabetes is significantly greater than the mean daily insulin dosage of patients with a family history of diabetes.

tion as previously for assessing the patients as to the severity of the diabetes, we found no significant difference in severity on the basis of insulin requirement of the patients with a family history of the disease as compared with the patients without such a history.

Obesity is reported as a factor which may contribute to the onset of diabetes. Using the table issued by the Association of Life Insurance Directors and the Actuarial Society of America as the basis for normal weights, the patients were divided into three groups.[5] This table allows for age, sex, height, weight, and average clothing. In investigating this complication, we considered as overweight patients who were 10 pounds or more above the accepted normal weight for their age, sex and height. In the same way, patients who were 10 pounds or more below the accepted normal were considered to be underweight. On the basis of this classification, 48 per cent of the patients were overweight and 26 per cent were underweight at the time they originally registered in the clinic. The incidence of obesity in our group of clinic patients was not as high as that reported by Joslin.[6]

The most prevalent complications encountered in the patients in this study are shown in table 11. In 29 per cent of the patients no major medical complications were

TABLE 11

Complications and diseases associated with diabetes

	Number	Per cent of total number of patients
Arteriosclerotic heart disease	63	32
uncomplicated	23	11
with hypertension	29	15
with coronary disease	6	3
with myocardial infarction	3	2
with arrhythmia	2	1
Hypertension	63	33
Retinopathy	44	23
Enlarged thyroid gland	33	17
hyperthyroidism	24	12
nontoxic enlargement	4	2
hypothyroidism	3	2
adenoma	2	1
Peripheral vascular disease	24	12
Gallbladder disease	16	8
Gastrointestinal disease	14	7
Enlarged liver	9	5

Note: The percentage column adds to more than 100 because some patients had more than one of the complications listed.

observed. The complications most frequently encountered were due to vascular disease and included arteriosclerotic heart disease, hypertension, peripheral vascular disease, or retinopathy. Of the 63 patients with arteriosclerotic heart disease, 3 had had myocardial infarcts, 6 had coronary sclerosis with some precordial pain, and 29 had hypertension as well as arteriosclerotic heart disease. None of the patients in this group had any history or evidence of rheumatic heart disease.

Of the 33 patients with enlarged thyroids, 24 had hyperthyroidism requiring in most instances thyroidectomy, 3 patients had hypothyroidism, 2 had adenoma of the thyroid with no disturbance in function, and in 4 patients there was nontoxic colloid enlargement of the thyroid gland.

In 16 cases, disease of the gallbladder was indicated by symptoms and confirmed by gallbladder X rays. In 9 of the patients enlargement of the liver not due to congestive heart failure was observed, and one of these patients had cirrhosis of the liver. In 14 of the patients some gastrointestinal disorder was observed, and in 2 of these patients X rays revealed duodenal ulcers.

In the group of 194 patients, 29 per cent had one of the complications listed in table 11, 21 per cent had two complications, and in 21 per cent three or four of the complications listed in the table were present.

The data in table 12 compare the patients without complications to those with complications as to present age, insulin requirement, age at onset of diabetes, and years of clinic attendance. The mean age of the patients without any complications was 52 years, as compared to

TABLE 12

Comparisons between patients having no complications or diseases associated with diabetes and patients having at least one complication or disease associated with diabetes

	Patients having no complications		Patients with at least one complication	
	Mean	Standard deviation	Mean	Standard deviation
*Present age	52	17	63	11
*Age at onset of diabetes	39	17	47	13
Present daily units of insulin	33	31	28	26
Years of clinic attendance	12	5	12	5

*The difference between the mean for patients having no complications and the mean for patients with complications is significant at the 0.05 confidence level.

63 years in the patients with one or more complications. The patients with complications developed their diabetes at a later age than did the patients with no complications.

In table 13 the time of onset of some of the complications as related to the onset of diabetes is reported. Of the patients with hyperthyroidism, 5 developed the complication prior to the detection of diabetes. In 16 cases, the hyperthyroidism occurred after the patient had had diabetes for some time. Retinopathy in all patients observed developed after the onset of the diabetes. It is difficult to collect absolutely accurate information as to the time of onset of hypertension or vascular disease. These conditions may occur without in any way disturbing the patient. The carbohydrate disturbance manifests

TABLE 13
Time of onset of specific complications relative to onset of diabetes*

	Analyzed by Diabetic Patients Who Have:							
	Hypertension		Retinopathy		Hyperthyroidism		Peripheral vascular disease	
	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent
Total number of patients having the complication	63		44		24		24	
Age at onset of the complication unknown	11		2		3		3	
Subtotal	52	100	42	100	21	100	21	100
Patients having the complication prior to onset of diabetes	17	33	0	0	5	24	1	5
Patients having the complication after the onset of diabetes	35	67	42	100	16	76	20	95

*The absolute time of onset of the diabetes may have preceded the clinical symptoms and the diagnosis, therefore this data is an approximation to the true situation.

itself with well defined symptoms and therefore may be the disease that brings the patient to the doctor.

In table 14, the relation of hypertension to the age of the patients at the time the study was done is shown. There were 63 patients with hypertension and 113 who were normotensive. In this group of patients, hypertension did not occur under the age of 40 years. The mean age at which hypertension occurred was 64 years. The mean age of the patients without hypertension was 58 years. The data indicate that hypertension is dependent upon age as well as upon the diabetes.

TABLE 14
Hypertension and present age

Present age	No. of patients		With hypertension		Without hypertension	
	Total	Per cent	No.	Per cent	No.	Per cent
	194	100	63	100	131	100
9 yrs. or less	1	1	0	0	1	1
10-19	3	1	0	0	3	2
20-29	5	3	0	0	5	4
30-39	5	3	0	0	5	4
40-49	17	9	3	5	14	11
50-59	45	23	15	24	30	23
60-69	74	38	25	39	49	37
70-79	40	20	20	32	20	15
80 and over	4	2	0	0	4	3
Mean			64		58	
Standard deviation			9		15	

Note: Fisher's "t" test indicates that the mean age of patients with hypertension is significantly greater than the mean age of patients without hypertension.

Table 15 shows the relation of the duration of the diabetes to the onset of retinopathy. Forty-four patients of the entire group studied had retinopathy. This complication occurred fairly early in the course of the disease. In patients who had retinopathy, diabetes was present in 18 per cent for less than six years. The incidence of retinopathy remained high and the decrease shown in patients with diabetes of more than 20 years duration was due to the fact that the majority of patients with this complication did not survive the disease for more than 20 years.

TABLE 15
Duration of diabetes at onset of retinopathy

Duration of diabetes	No.	Per cent
	44	100
2 yrs. or less	3	7
3-5	5	11
6-8	8	18
9-11	9	21
12-14	3	7
15-17	4	9
18-20	7	16
21 and over	3	7
Unknown	2	4

In table 16 are shown the age of onset of retinopathy and the relation of this to hypertension. The table also shows the incidence of hypertension in the group with retinopathy. In the 44 patients with retinopathy, 23 did not have hypertension and 21 did have hypertension. The mean age at which patients without hypertension developed retinopathy was 55 years. The mean age at which patients with hypertension developed retinopathy was 61 years. The Fisher "t" test shows no evidence that the mean age at onset of retinopathy in patients with retinopathy and hypertension was significantly greater than the mean age of the patients with retinopathy and without hypertension. This is interesting because it suggests that in the diabetic patient hypertension per se is not the etiologic cause of the retinopathy.

Table 17 gives the correlation coefficients based on the data of the 56 patients in the group in whom no other disease was present. As was true in the larger group of 331 patients, there is a significant negative correlation between the severity of the diabetes, as measured by the daily insulin requirement and the age of onset of the diabetes. This correlation coefficient is significant whether or not allowance is made for the duration of clinic attendance. It indicates clearly that on the average the older the age at which the diabetes develops, the less severe it is.

In table 18 the relation of the complications to the sex of the patient is given. There were more females

TABLE 16
Hypertension and the age at onset of retinopathy

Age at onset of retinopathy	Total no. of patients with retinopathy		Patients without hypertension		Patients with hypertension	
	No.	Per cent	No.	Per cent	No.	Per cent
	44	100	23	100	21	100
9 yrs. or less	0	0	0	0	0	0
10-19	1	2	1	4	0	0
20-29	0	0	0	0	0	0
30-39	1	2	1	4	0	0
40-49	6	14	5	22	1	5
50-59	14	32	6	26	8	38
60-69	17	39	10	44	7	33
70 and over	4	9	0	0	4	19
Unknown	1	2	0	0	1	5
Mean			55		61	
Standard deviation			13		11	

Note: A "t" test shows no evidence that the mean age at onset of retinopathy of patients with retinopathy and hypertension is significantly greater than the mean age at onset of retinopathy of patients with retinopathy and without hypertension.

TABLE 17
Correlation coefficients based on data of 56 patients having no complication or disease associated with diabetes.
The following correlation coefficients measure relationships between two or more of the following variables:
Present daily insulin dose Initial daily insulin dose
Age at onset of diabetes Length of clinic attendance

	Coefficient of correlation	
	Linear	Partial
*Present daily insulin dose—age at onset of diabetes	—.43	
*Present daily insulin dose—age at onset of diabetes, after removing the effect of years of clinic attendance		—.42
Present daily insulin dose—years of clinic attendance	.15	
Present daily insulin dose—years of clinic attendance, after removing the effect of age at onset of diabetes and initial daily insulin dose		.19

*Significantly different from zero at the .05 level of significance.

than males in this group of patients. A greater proportion of the patients who developed complications were females than would be expected from the total sex distribution. This was particularly striking in the patients developing thyroid disease and in the patients developing hypertension. The chi-square test shows that hyperthyroidism and hypertension are statistically related to the sex of the patient. The fact that a greater proportion of female patients had thyroid disturbance is not surprising, but the higher incidence of hypertension in the female sex is different from what would be expected from the nondiabetic population.

Table 19 shows the severity of the diabetes, based on the daily insulin requirement. The diabetes was more severe in the patients with hyperthyroidism and in the patients without complications than in the patients de-

TABLE 18
Relation of complications to sex

Sex	No. of patients		No Complications		Hypertension		Retinopathy		Hyperthyroidism		Peripheral vascular disease	
	Total	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent
	194	100	56	100	63	100	44	100	24	100	24	100
Male	72	37	25	45	15	24	15	34	4	17	9	38
Female	122	63	31	55	48	76	29	66	20	83	15	62

Note: The following complications were found to be statistically related to the sex of the patients by the chi-square test: hyperthyroidism and hypertension.

TABLE 19
Relation of complications to the present severity of the diabetes

Present severity of diabetes	No. of patients		No Complications		Hypertension		Retinopathy		Hyperthyroidism		Peripheral vascular disease	
	Total	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent
	194	100	56	100	63	100	44	100	24	100	24	100
Mild	40	20	15	27	11	17	7	16	4	17	6	25
Moderate	23	12	2	3	8	13	8	18	2	8	4	17
Moderate-severe	44	23	10	18	17	27	12	27	4	17	6	25
Severe	87	45	29	52	27	43	17	39	14	58	8	33
Mean present daily insulin dosage	29		33		27		25		37		20	
Standard deviation	28		31		24		30		35		22	

veloping the degenerative lesions.

Analysis by the chi-square test showed that retinopathy and hypertension, retinopathy and peripheral vascular disease, and hypertension and hyperthyroidism occurred as multiple complications more frequently than would be expected by chance alone.

DISCUSSION

The data on a large group of patients actively attending the Diabetic Clinics of the Third (New York University) Medical Division of Bellevue Hospital have been analyzed statistically in considerable detail. The statistics are on living patients, and all the patients were seen during the study. The physicians caring for these patients had been working in the clinics for 5 to 25 years.

The most significant and interesting points brought out by the study of 331 patients are: the predominance of the elderly female diabetic attending this clinic, the large number of patients who used the facilities of the clinic over many years, and the relationship of the severity of the diabetes to the age at onset.

In the study of the group of 194 patients who had attended the clinic for 5 years or more, the factual data showed them to be very similar to the larger group of 331 patients. In the group of 194 patients, it is significant that the onset of diabetes was at a younger age in patients with a family history of diabetes. However, the data show no difference in the severity of the diabetes between patients with a family history of diabetes and those without a family history of diabetes.

Only 29 per cent of the 194 patients were free from complications, and multiple complications were extremely common.

The present age of patients having no complications associated with their diabetes was significantly lower than the age of patients with at least one complication. The incidence of complications appeared to be more closely related to the actual age of the patient than to the duration of the diabetes.

The age of onset of the diabetes is significantly higher for those patients with at least one complication.

Retinopathy and hypertension occur frequently in diabetic patients. Hyperthyroidism and hypertension were relatively more prevalent in the female than in the male diabetic.

It is obvious that the carbohydrate disturbance in the diabetic patient is only one aspect of the disease. This is well controlled by the administration of insulin but insulin therapy does not control the onset of the degenerative lesions in the young diabetic. Mirsky[7] has pointed out that in many patients "the various manifestations of the degenerative lesions are apparent by the time the glycosuria is discovered." It is difficult on the basis of statistical analysis to know which actually comes first in the older patient. One fact is clear; diabetes, as well as being a disturbance of carbohydrate metabolism, is also a general metabolic disturbance. In the patient developing diabetes at an early age, the carbohydrate disturbance tends to be more severe than in the patient who develops diabetes over the age of 50. These young diabetics appear to age more rapidly than do nondiabetic subjects. The aging manifests itself in the vascular degenerative lesions that occur. In the individual who develops his diabetes late in life it would appear that the carbohydrate disturbance is part of the aging process.

It is, we think, difficult to determine whether the vascular lesions precede, accompany, or follow the carbohydrate disturbance. The difficulty in this instance is due to the fact that in the older age group the diabetes is often so mild that it does not cause the classical symptoms. This makes it difficult to establish definitely the relative onset of the diabetes. In table 13 we have estimated the time of onset of diabetes and the time of onset of the complications. The tendency is for the complications to be diagnosed after the onset of the symptoms of diabetes.

SUMMARIO IN INTERLINGUA

Curso e Complicationes de Diabete Mellite

Esseva analysate le curso e le complicationes de diabete mellite in un gruppo de 331 patientes qui visitava regularmente le Clinicas Diabetic del Tertie Division Medical (Universitate New York) del Hospital Bellevue. Le etates del patientes al tempore del studio variava ab infra 9 a supra 70 annos. Femininas de etate avantiate representava 32 pro cento del gruppo total. Le duration del morbo in le casos individual variava ab 1 a 34 annos. Insulina esseva requirite per 70 pro cento del patientes. Es presentate datos relative al quantitate e al typo de insulina usate. Le severitate del morbo esseva evalutate super le base del numero de unitates de insulina requirite: leve — diabeticos qui non prendeva insulina; moderate — diabeticos qui prendeva usque a 15 unitates per die; moderatemente sever — patientes qui prendeva inter 15 e 30 unitates per die; sever — illes qui prendeva plus que 30 unitates per die. Secundo iste classification, 114 casos esseva sever e 76 moderatemente sever.

Cento novanta-quatro patientes habeva visitate le Clinica durante plus que 5 annos. Istes esseva studiate plus detaliatemente. Quaranta-duo de illes habeva un historia familial de diabete. Le severitate del diabete monstrava nulle relation a si o non le morbo esseva hereditari. Nos summarisa le plus frequente complicationes incontrate

in iste patientes. Dece-septe pro cento habeva allargate glandulas thyroide; inter istes, 12 pro cento habeva hyperthyroidismo. Iste frequentia es plus alte que illo reportate per altere observatores. Esseva etiam determinate le tempore del declaration del complicationes in relation al tempore del declaration de diabete. Le plus commun complicationes esseva hypertension, retinopathia, e arteriosclerotic morbo cardiac. Le 194 patientes sub observation durante plus que 5 annos includeva 63 con hypertension e 44 con retinopathia. Solmente 29 pro cento del patientes esseva libere de complicationes. Le etate del patientes al tempore del declaration de diabete esseva significativemente plus alte in casos con al minus un complication.

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Normal Fat Requirement

The question of the exact amount of fat which is optimal for a normal dietary remains controversial. The major portion of the information available has been obtained from statistical studies of the problem and it is only within relatively recent years that it has been clearly established that *some* quantity of fat, or lipid material, is necessary in the diet. Although fat and carbohydrate can replace each other in isodynamic proportions within wide limits, other considerations must make necessary some qualification of this property of neutral replacement. The feeling of satiety following a high fat meal is a common experience. Due to the slower absorption of fat from the intestine, this foodstuff appears to be available to the organism over a protracted period of time and to increase the so-called "staying power." The extensive replacement of fat in the diet by carbohydrate is limited by the stuffing process that is necessary and the consequent discomfort to the individual which is often accentuated by carbohydrate fermentation in the intestine. Starling stated in 1918 that the people of England lost weight rather than eat more of high-carbohydrate diet made necessary by the shortage of fat in the First World War.

Atwater proposed that in a standard dietary suitable for the average adult, fat should represent 33 per cent of the total of 3,500 calories. Murlin has reported that in the diet of the United States Army soldier in training camps during the First World War, fat represented 31 per cent of the total energy (about 3,700 calories) consumed. In World War II fat represented about 40 per cent of the total caloric intake of the American soldier. During this war, the Committee on Fats of the National Research Council recommended that, in the rationing of foodstuffs, the fat supply should not be reduced below 80 gm. per person per day.

From the book *Diseases of Metabolism* edited by Garfield G. Duncan, M.D., published by W. B. Saunders Company, Philadelphia, 3rd ed., 1952, Section "Lipid Metabolism" by Abraham White, Ph.D., pp. 197-98.

Fluids and Electrolytes in the Therapy of Diabetic Acidosis

Panel Discussion

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Moderator

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MODERATOR HOWARD: Dr. Osler used to say that anyone who knew syphilis knew medicine because the wide variations in the late complications required the physician to know something about nearly every field of medicine. Since late complications of syphilis are now relatively rare, I think diabetes has taken its place and the physician who tries to take care of diabetics must know something about all the medical specialties.

The most serious disturbances of water and electrolyte metabolism occur in association with diabetic acidosis, and result directly from the metabolic defect of insulin deficiency. Many patients in acidosis present coincident abnormalities in other areas, such as renal disease, heart failure, septicemia and the like, which must be given due consideration in planning the course of therapy. In order to highlight the water and electrolyte problems, we have felt it wise to eliminate such complications, at least in the first portion of this panel discussion, in our hypothetical patient who is to be treated.

We shall consider, then, the case of a middle-aged man whose normal weight is 70 kg., and we shall assume that he has received a dosage of insulin which is adequate according to the scale which you happen to prefer; that is, he has been given either a whacking dose intravenously or a reasonable dose subcutaneously. But we will assume for the moment that there is an adequate supply of insulin in his circulation to counteract and begin to reverse the factors which have put him in the situation in which he now finds himself. Assume that this individual has a blood sugar of 700 and that his plasma carbon dioxide is 10 mEq. per liter or 22 volumes per 100 cc. He has lost about fifteen pounds in weight during the period in which he has developed this episode of coma, a matter of four or five days.

Dr. Danowski, with these premises—you have made a physical examination and found nothing else wrong—will you tell us what you think about how this man has lost these fifteen pounds and the relative compartmental losses of electrolytes which you think he may have suffered so that we may know the status of this patient at the beginning of treatment.

DR. DANOWSKI: This can be answered most readily by referring to published studies of amounts of therapeutic ingredients which were retained during the course of successful therapy. I should like to cite the studies of Atchley, of Butler, of Darrow, and of Nabarro in addition to my own studies.

The range of water deficits reported by these various

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workers extended from 4.5 to 8 liters. The higher figure approaches Dr. Howard's estimated fifteen-pound weight loss. The chloride loss in these five groups of studies, as indicated by repletion, ranged from less than 10 gm. to 50 gm., expressed as sodium chloride. The sodium loss was somewhat greater, extending from 20 to 60 gm. The potassium deficits varied from 27 to 33 gm. The nitrogen losses ranged as high as 62 gm.

This gives us a series of perimeters at which we can shoot in terms of replacement and corrective therapy.

MODERATOR HOWARD: We now have an approximation of what this individual has lost. Dr. Knowles, would you like to tell us how you would start fluid and electrolyte replacement therapy in this case?

DR. KNOWLES: Dr. Danowski has listed the range of deficits found in the average case. I think the first principle to remember is that these deficits are not to be replaced all at once. In an infant, dehydration may be corrected rapidly but in an adult, correction must progress in more leisurely fashion.

Many different methods of treatment have been published. Some recommend the use of bicarbonate solution immediately, others chloride, some glucose, and others fructose. To satisfy all authorities, one would have to administer several different intravenous infusions at once.

At the Cincinnati General Hospital we have rough rules to determine fluid administration in the first six hours of treatment. One might say that you have music to play with in the first six hours; after that you have to play by ear. To begin with, in the average case it is appropriate to give in the first six hours fluid volume equal to approximately 5 per cent of the body weight. In the 70 kg. or 150 pound man, this would entail the administration of 3 to 4 liters of fluid. This fluid is usually given as saline, so that the patient would receive about 27 gm. of salt. The first liter may be run in during the first hour, the second liter during the second and third hours, and the third liter in the succeeding three hours.

When should glucose be added? Probably in the second or third liter, or perhaps not until the sixth-hour period, depending upon the height of the initial blood sugar level. This man's blood sugar is 700 mg. I suggest giving the third liter as 5 per cent glucose in saline, or perhaps holding off glucose until the end of the six-hour period.

If sodium bicarbonate is easily accessible, there are sufficient theoretical reasons to warrant its use. A feasible plan would be to administer the first 2 liters of isotonic sodium as ⅔ chloride and ⅓ bicarbonate. The above solution may conveniently be made up by adding one ampule of 3.75 gm. of sodium bicarbonate, which is about 45 mEq., to 600 cc. of saline, and making up to one-liter volume with distilled water or 5 per cent glucose. The latter would give about a 2 per cent glucose solution, which I do not think is detrimental with an initial blood sugar of 700 mg.

For this patient I, therefore, would recommend the first 2 liters as isotonic sodium, ⅓ bicarbonate and ⅔ chloride, and the third liter as saline, possibly with 5 per cent glucose added. After the first six-hour period, fluid therapy will vary according to estimation of the physiological derangements.

MODERATOR HOWARD: I might ask Dr. Knowles one question myself: Most of us when we see a patient in diabetic acidosis haven't the mathematical acuity to make these calculations which he has proposed and haven't Otto Folin at hand to tell us about this and that. Would it be fair to say that if you were in a place where only normal salt solution were available that you would use this for the first liter or two in your therapy?

DR. KNOWLES: Yes, Dr. Howard. I think that saline, in most cases, will do as well as the bicarbonate chloride mixture. I might say that I would certainly use bicarbonate if I thought the patient had renal damage or poor renal reserve, and if I were uncertain about the ability of the kidney to form sodium bicarbonate.

MODERATOR HOWARD: I think in all probability no two individuals on this panel would treat the same patient under the same circumstances in exactly the same way. I believe, however, that they would act on almost identical principles.

I think it only fair to ask other members of the panel if they have any comments in regard to Dr. Knowles' recommendations.

DR. LUKENS: I am impressed with Dr. Seymour Kety's work on coma. In connection with alkali and acidosis, he made this point: A very small amount of alkali will correct the low blood *p*H. The low carbon dioxide need not be corrected with alkali; if that small help from alkali is given to the patient he will do well. Consequently, we have adopted the policy of giving a very small amount of alkali promptly but we do not attempt to restore the plasma carbon dioxide by this means.

DR. DANOWSKI: I certainly agree with Dr. Lukens. Most of our patients, however, do not receive bicarbonate. We like to use the rise in carbon dioxide as an index of the patient's progress. As a consequence, if the *p*H is not greatly reduced, we treat the patients only with sodium salt. In using sodium chloride, one must keep in mind that chloride is present in a higher proportion in physiological saline than in the body. If one relies solely on 0.9 per cent sodium chloride for rehydra-

tion one may end up with a hyperchloremic acidosis. This problem can be resolved by diluting the so-called physiologic saline down to a more hypotonic solution. Though this can be done in vitro, we prefer to accomplish it by the infusion of 5 per cent glucose in water once the blood sugar has begun to decrease.

DR. SPRAGUE: Perhaps some distinction should be made between the use of sodium lactate or bicarbonate as alkali and their use for the purpose of reducing the concentration of chloride in the solution. We have been anxious to avoid the use of unphysiologic concentrations of chloride, for the reasons which Dr. Danowski just mentioned; and so, as a means of preparing solutions with a lower concentration of chloride, we have resorted to the use of either sodium lactate or bicarbonate.

Nevertheless, fairly rapid infusion of sodium bicarbonate is occasionally justifiable. Suppose, for example, we have a patient with a myocardial infarction who is hyperventilating because of acidosis. Such hyperventilation may involve a great deal of muscular work. There may be much to be gained by correcting his acidosis rapidly and thereby stopping the hyperventilation. The infusion of an unusual amount of alkali under those circumstances may be justifiable.

MODERATOR HOWARD: I might ask the panel one question from the point of view of practicality. In the good old days before we knew so much about the fall in potassium and this and that, we did overtreat everyone with sodium chloride solution and often ended with hyperchloremic acidosis. But that did not seem to make the mortality rate change a great deal; rehydration was the end gained. The greater danger is failure to give any solution in the absence of one of these ideal solutions. Where only sodium chloride was used the electrolyte pattern did adjust itself in the end when the patient began to eat and the kidneys resumed their function.

To give sufficient water seems to be more important. Special solutions are idealistic and should be used as indicated. Would you all agree with that? (No dissent)

At this point a twofold question should be considered. First, when do you add sugar to your solution? Do you administer sugar? What do you think about the idea of adding sugar right at the start and bringing about a further rise in the blood sugar with the idea of getting a head of chemical pressure to achieve rapid formation of glycogen?

DR. LUKENS: I do not recommend starting intravenous administration of glucose in the first four hours.

DR. DANOWSKI: Neither do I.

DR. SPRAGUE: Nor I.

DR. KNOWLES: Nor I.

MODERATOR HOWARD: I suspect that any of these gentlemen would give it, however, if in the first hours their insulin has reduced the blood sugar to 10 mg.

DR. KNOWLES: Dr. Howard, may I make a comment? Juvenile diabetics may occasionally develop a ketosis which is a little different from that of adults in that rapid ketoacidosis can occur six to eighteen hours before there is a significant hyperglycemia and dehydration. The blood sugar may be 200 mg. with a carbon dioxide content of 10 mM/L. Such patients should receive glucose from the start of therapy or an insulin reaction may supervene.

MODERATOR HOWARD: The second question is also in regard to the administration of sugar. Is fructose better than glucose? Is there any advantage in using it? If so, why?

DR. LUKENS: Several things ought to be kept in mind when one thinks about fructose in diabetic acidosis. In the first place, fructose is not a substitute for insulin. Whatever fructose will do to liver glycogen in the absence of insulin, it is no substitute for insulin in the patient in coma.

Although there is less glycosuria after fructose than after equal amounts of glucose there is no fall in ketones and as far as we know there is no nitrogen retention in the absence of insulin. Fructose does not correct all the major defects of diabetes; so whatever fructose does, it is only an adjunct and is dependent upon the presence of insulin.

Another point is this: Fructose for some mechanism which I do not understand does not cause as much water retention when given by the vein or under the skin; and there is less disturbance of the water metabolism in that sense. So there are really some very minor reasons for using it, but it never bypasses the essential demand for insulin.

DR. DANOWSKI: The fructose will enter the glycolytic cycle without the intervention of insulin. The difficulty is that most of the fructose gets into the liver as glycogen and then comes out as glucose. However, because it is such a good glycogen former, fructose tends to minimize ketone body production in that sense, because it is the deglycogenated liver which produces ketone bodies.

As Dr. Lukens has pointed out, the reabsorption of sugars in the kidney tubule is nonadditive; and, if one uses a mixture of glucose and fructose, there will be less glycosuria.

MODERATOR HOWARD: Dr. Sprague, in making your comments will you answer specifically a question from the floor. Is there any *harm* in giving fructose?

DR. SPRAGUE: I suppose one might summarize his opinion about fructose by answering the practical question, "Do you use fructose?"

My associates and I have not been using fructose in the treatment of diabetic acidosis. My over-all evaluation of the evidence forces me to the conclusion that any therapeutic benefits from administration of fructose are slight, if they exist at all.

In answer to the question which Dr. Howard just proposed, I think the answer is yes; there are potential dangers in the early use of fructose, just as in the early use of glucose. One of the outstanding disadvantages, if one infuses a large amount of fructose, is the hypertonicity one produces in the extracellular space, with consequent aggravation of cellular dehydration.

DR. KNOWLES: My experience with fructose is limited, in fact limited to three cases in which it was used consecutively. These three patients were admitted with moderately severe keto-acidosis and each developed symptoms of hypokaliemia greatly in excess of what one would have expected clinically. I wondered if the rapid entrance of fructose into the liver brought about hypokaliemia sooner than one is accustomed to seeing it.

DR. DANOWSKI: Perhaps this is an argument for fructose, rather than against it; perhaps it does expedite recovery. I do have a feeling, though, that actually you may save a little bit on insulin if you use fructose, but you do not know how much insulin to use anyhow.

DR. SPRAGUE: Fructose is very cheap now, too.

MODERATOR HOWARD: No plugging for the drug houses. (Laughter)

Another question submitted is: How much is fructose now being used in the treatment of coma? That question I suppose has been discussed. The members of this panel do not seem to use it at all. Dr. Danowski suggests that we ask those in the audience who do use fructose to show their hands—there are some, but the number is far less than I would have guessed from the literature. Maybe this august panel here has kept down some hands. (Laughter)

I think we ought to turn now to a discussion of potassium. There can be little doubt now that under certain circumstances, at least during the ordinary treatment of acidosis, the serum potassium may fall to a low level, and although early administration of glucose may exaggerate and hasten the onset of hypokaliemia, the serum potassium may fall to a dangerously low level in patients who have received no glucose whatever.

Dr. Danowski, when would you give potassium? What should be the rate of administration? What are the dangers of its use?

DR. DANOWSKI: The potassium which is lost in the urine in the development of coma comes largely from cells. It comes out of the cells because there is interruption of carbohydrate metabolism, deglycogenation of the liver, dehydration of the cells, and breakdown of body protein. All of these processes release cell potassium into the extracellular fluid.

The extracellular concentrations are in turn determined by the rate at which potassium is released by cells, the rate at which it is lost in urine and in vomitus, and the degree of extracellular dehydration. On admission the seriously ill coma patient usually has hyperkaliemia, though normal or low values may be present in the milder cases and especially in those who may have been given insulin just before transfer to the hospital.

Once therapy with insulin and potassium-free solutions has been started, the trend of potassium transfers is reversed, body fluid volumes are expanded, and the level of serum potassium begins to decrease. Potassium replacement can then be started after the second or third hour provided that toxic levels are no longer present, that the patient is putting out adequate amounts of urine, and that the electrocardiogram shows no evidence of peaking of the T wave. For this purpose, a potassium salt should be given intravenously. One cannot administer solutions more concentrated than 80 mEq./L. without producing spasm or pain.

The potassium salt should be phosphate in most instances because, as already pointed out, sodium chloride solutions already provide too much chloride. The use of potassium chloride aggravates this discrepancy. However, there is no conclusive evidence that phosphate replacement at this point is essential, although it is reasonable and safe.

How much can one give? We know that a patient with a serum potassium level of 4 mEq./L. has a total of 60 to 80 mEq. of potassium in the extracellular fluid and that raising the concentration twofold or threefold produces cardiac standstill. Hence, if one were to give such a patient 60 or 80 mEq. of potassium in zero time, one would produce cardiac standstill. We therefore start therapy with a solution of 40 mEq. of potassium per liter and administer it not in zero time, but at a rate of 500 cc. per hour. This allows some of the potassium to go into cells during glycolysis, reglycogenation, rehydration, and protein formation. These transfers together with concurrent losses in urine eliminate risk of producing potassium intoxication. This rate of administration can be continued until such time as oral intake can be resumed. This is usually possible somewhere between the sixth and twelfth hours of therapy. At that time potassium can be given by mouth at a rate of 1 gm. of the salt every four hours.

MODERATOR HOWARD: Have any other members of the panel any comments to make upon these preliminary remarks?

DR. LUKENS: I want to ask Dr. Danowski whether one can give as much as 4 gm. of potassium chloride, intravenously, not too rapidly, without danger. Is that a rule of thumb which is worth having, or is it all wrong?

DR. DANOWSKI: That is right. One can give some where around 40 mEq., not in zero time. This is roughly 4 gm.

MODERATOR HOWARD: Dr. Sprague, will you answer a very intelligent question from the audience? Isn't there an enormous variation in the acceptance of potassium from patient to patient? That certainly has been my experience.

DR. SPRAGUE: Dr. Howard, you have already answered it; the answer is yes. Also, Dr. Danowski's studies of the amount of potassium retained during recovery from diabetic acidosis indicate a very large variation between individuals. Because of this variation and the hazards associated with administration of large amounts of potassium, it has been our practice to stay on the conservative side and give it at the rate of about 25 mEq. per hour, starting around the fourth hour.

MODERATOR HOWARD: How do you evaluate the need for potassium, therefore the speed of administration?

Dr. Knowles commented on the use of potassium in general. Will you begin a discussion of this question? Do you determine the need for potassium by the use of the electrocardiogram or by the level of serum potassium? Or do you do it by hunch?

DR. KNOWLES: Dr. Howard, this may be one of the situations where one has to play by ear instead of reading from the music.

Ideally, it would be helpful to have all possible methods of evaluation. I believe the electrocardiogram is of great value provided there is no myocardial disease. The electrocardiogram has in our experience proven its worth, not only in frequently determining the presence of a deficient state, but particularly in the management of the case in which we are rapidly administering a great deal of potassium intravenously.

If determinations of the serum potassium are available, it may be helpful to have them done at six-hour intervals. Finally, one must not neglect the clinical appraisal of the patient. He must be followed carefully for changes in reflexes, respiration, and so forth.

In incidences where severe symptoms of hypokaliemia have developed, I have administered as much as 20 gm. of potassium chloride over a twelve-hour period in order to keep reflexes present. During such intravenous administration, the electrocardiogram is of marked value as a guide to prevent overdosage. Tracings may need to be taken every 15 to 30 minutes, using the lead where the depletion pattern was best shown initially. One may start potassium chloride at the rate of 1.0 gm. per half hour till the neurological picture improves, and then slow down to 1.0 gm. per hour or more depending on serum concentration and electrocardiographic findings. The neurological status will usually revert towards normal before the electrocardiogram shows significant change. The presence of uremia or oliguria would, of course, temper considerably the amount of potassium to be given.

In summary, then, in the severely depleted person, I think that all three methods of evaluation, the serum concentration, the electrocardiogram, and the physical status are needed properly to manage the patient.

MODERATOR HOWARD: I might mention that hyperkaliemia and hypokaliemia produce the same muscular defect. You may often see the amazingly shallow respiration so that you do not even know the patient is breathing in both hyperkaliemia and hypokaliemia. The electrocardiogram, however, will make the distinction between these two conditions.

The last question on this particular subject is important. Can one or should one give potassium when the serum potassium is normal, if the electrocardiogram shows evidence of hypokaliemia? I think this is a difficult question since no one really knows where the potassium defect lies, that is, does the neuromuscular defect of hypokaliemia result from low serum potassium per se, from low intracellular potassium, or from an abnormal ratio between the two?

DR. SPRAGUE: This is a difficult question as Dr. Howard says. In actual practice, when one is depending upon flame photometer determinations of the serum potassium as a guide to therapy, and encounters normal values, I ordinarily do not administer potassium. On the other hand, when one is being guided by the electrocardiogram and finds evidence of hypokaliemia and knows nothing about the actual level of the serum potassium, I do give potassium. In other words, for better or for worse I am guided by whatever type of measurement I have.

DR. HOWARD: Suppose you had both; suppose your serum potassium is six and your cardiogram indicates a deficit.

DR. SPRAGUE: That is a hypothetical question. (Laughter) I should be inclined not to give potassium under such circumstances.

DR. LUKENS: I should be inclined not to give it too; but I think this might be considered. The time course-of-events would be very much in one's mind. If this electrocardiogram and serum potassium were taken six or eight hours after insulin had been first given so that an impending fall in potassium was possible at that time

in the treatment, one might feel that it was proper to anticipate the fall by giving a little potassium to save the heart.

DR. SPRAGUE: That is the first time I ever knew Dr. Lukens to be a middle-of-the-roader on anything. (Laughter)

DR. DANOWSKI: I should like to comment on Dr. Knowles' previous statement that he tends to become conservative as therapy continues.

I like to be conservative at the start of therapy and really speed up the rate of potassium administration later on because this can be done quite safely. All of these patients have a potassium deficit, and it is generally accepted that survival depends in part upon adequate repletion. However, one does not have to produce complete repletion early in therapy. All that is needed is to move that patient along toward recovery.

MODERATOR HOWARD: I think you have heard conservative and wise statements on this subject.

Other questions are: Does one need to give phosphate for replacement therapy before the patient is able to eat? In other words, during the period of parenteral therapy, should one add phosphate? Dr. Knowles, would you like to answer these questions?

DR. KNOWLES: I cannot answer specifically about phosphate. From my reading of the balance studies which Dr. Danowski quoted, I am not sure that there is an actual negative phosphorus balance. On the other hand, during the first eighteen to twenty-four hours of the recovery period, or in the next day or so, the serum phosphorus concentration may fall to as low as 0.2 mg. per cent, suggesting that some part of the body is hungry for phosphorus. I do not feel there is enough evidence at present to state that phosphorus should be administered routinely in the treatment of diabetic acidosis.

MODERATOR HOWARD: I think the deficit has been clearly shown in your own laboratory by Dr. Guest. There is a deficit, but its necessity in early replacement is the doubtful point.

DR. SPRAGUE: I agree that it has never been demonstrated that this large deficit of phosphorus (which I agree is present) is of clinical significance, or that repletion of it is of importance in saving the patient. On the other hand, I think more and more men who treat diabetic coma are becoming impressed with the extremely low level of serum inorganic phosphate which is encountered after a few hours of treatment. Sometimes the serum phosphate is so low that no measurable inorganic phosphate can be demonstrated in the serum. Many men, including my associates and I, have been administering some inorganic phosphate along with the potassium.

DR. DANOWSKI: I administer phosphate as the potassium salt, but not in the belief that it represents an essential replacement item. There is no evidence, even in these patients to whom Dr. Sprague has referred, that the very low level of serum inorganic phosphorus impedes recovery or produces any symptoms. It is rather surprising, in view of the magnitude of the deficit and the important role which this ion plays in carbohydrate disposal to find that there is no clinical evidence of a deleterious effect resulting from losses of phosphate.

MODERATOR HOWARD: Some of the questions from the audience bring us now to certain other rather interesting complications of therapy.

We started with a man who had no troubles other than the state of acidosis originally defined, but now in cases in which death occurs in acidosis the cause of death may be a variety of conditions. One question concerns shock. Certainly shock is the commonest complication. The evidences of shock are a fall in blood pressure, rapid pulse, and poor circulation. Dr. Lukens, will you discuss this situation?

DR. LUKENS: I begin by thinking of a lesson about medical shock which I learned from Dr. Issac Starr. He said, "If you ever have to cut down on a vein to get blood or to insert a needle, the patient needs blood or plasma."

One actually sees that in a certain number of cases of advanced coma. The extremely cold extremities and the fall in blood pressure will be quite apparent. There is just one other criterion which I use which is not in any of the books and which is 100 per cent unofficial. In a series of cases of coma reported with Dr. Helen Martin some years ago, 100 per cent of the patients with blood sugar above 800 had low blood pressure; and the blood sugar of 500 or higher may very well mean the beginning of defective renal clearance due to circulatory failure. If this is a useful warning of shock, we shall all be glad to take it.

DR. DANOWSKI: I believe that any patient who has a fully developed coma has some measure of circulatory inefficiency. This arises from the huge deficits of extracellular water and salt. The presence of a normal blood pressure does not exclude this because increased peripheral resistance will keep the blood pressure up at the expense of a decrease in the circulation to the organs. While trying to replace these deficits, there is some advantage to expanding the depleted plasma volume. Though blood or plasma can be used, I myself prefer dextran because it is readily available and safe. I routinely infuse 500 cc. of 6 per cent dextran. If the patient is in profound circulatory collapse, more intensive therapy is employed.

MODERATOR HOWARD: Dr. Sprague, what is your opinion about shock?

DR. SPRAGUE: I agree with Dr. Danowski's statement that patients in coma are all in shock if one defines shock as he did; and I think this is a reasonable thing to do.

Dr. Howard himself made an observation about the early detection of shock which I think is sometimes helpful. He observed that if, after administration of several liters of fluid intravenously, the hematocrit does not start to fall, one can suspect that the administered fluid is running out of the vascular space, so to speak, and shock is developing.

I have not treated shock routinely with dextran, as Dr. Danowski suggested. Rather, I have treated it when it has become clinically apparent in the form of a serious drop in the blood pressure, and I have usually employed plasma or whole blood.

DR. KNOWLES: I want to make one comment on the use of levophed in the treatment of shock in diabetic coma. When shock does not respond first to fluids, then to plasmic expanders or blood, levophed may be life-saving. I should say that my associates and I have saved six lives with it over the past two years. In one instance, a woman was unable to maintain her own blood pressure without levophed for four days, and she ultimately survived. The dose has usually been 1 to 2 mg. per hour.

MODERATOR HOWARD: If a patient who has had urine in his bladder on admission thereafter has little or no excretion of urine, how does this influence your management of diabetic acidosis? I shall ask Dr. Danowski to discuss this question since he is writing a book on the subject.

DR. DANOWSKI: In a patient who no longer secretes urine after catheterization has emptied the bladder, one should think first of anuria on the basis of circulatory collapse, and secondly of acute tubular damage, that is, so-called lower nephron nephrosis secondary to an earlier bout of circulatory collapse. There are numerous such cases in the older literature.

MODERATOR HOWARD: Suppose the individual already has rather serious renal disease. Let's say he has a nephrotic syndrome and is already edematous. Under these circumstances should you administer more fluid and electrolytes or should you simply limit the treatment to insulin and try to take care of the primary defect alone?

DR. DANOWSKI: If the patient has pre-existing renal disease, one cannot administer large amounts of fluid to these patients on the assumption that the kidneys will make the necessary excretory adjustments. Under those circumstances therapy has to be far more custom-tailored than it is in the run-of-the-mill case of diabetic coma.

MODERATOR HOWARD: Two other complications might be mentioned briefly. When one pours in fluid and electrolytes one has to think of possible harmful effects such as pulmonary edema. How to prevent this I do not know but early detection may perhaps be helped by watching the veins in the patient's neck or by repeated tests of the venous pressure. Gastric dilatation is another complication which should be watched for.

Questions have been asked about the administration of sodium solutions postoperatively. Many surgeons fear giving salt to diabetic patients. What is your opinion, Dr. Knowles?

DR. KNOWLES: The administration of sodium postoperatively in the diabetic should not be any different from that in the nondiabetic patient.

MODERATOR HOWARD: Would you give any sodium, or withhold it for three or four days?

DR. KNOWLES: It all depends upon the degree of operative stress. If it is a simple procedure, I should say their sodium intake should be normal; if it is some severe type of operation, then sodium should be given in minimal amounts, maybe a gram or two daily, for two or three days.

DR. SPRAGUE: I wonder if this fear of sodium is not in part a carry-over from the days when the routine treatment of surgical patients used to include three or four liters of physiological solution of sodium chloride a day. Patients who were so treated inevitably had difficulties with pulmonary edema, overhydration, and so on. Perhaps this swing to no sodium at all represents a sort of rebound from the previous use of excessive quantities of sodium.

Sodium, like anything else, is to be feared if it is given in excess, but I should agree with Dr. Knowles that there is really no basis for difference in the administration of sodium to diabetic and nondiabetic patients after operations, providing one is not dealing with complications such as acidosis or renal insufficiency.

DR. DANOWSKI: It is useful to recall that the sodium we excrete today is, in the net sense, sodium we took in excess yesterday or the day before. If a patient is started on a diet with no sodium in it whatsoever, such as the rice diet, in a matter of about three days the urine becomes sodium-free. A patient can therefore continue on a low sodium regimen for weeks, for months, or for years without developing sodium depletion, provided that extrarenal losses of this ion do not occur.

The argument insofar as the postoperative use of sodium in nonsodium depleted patients is concerned narrows down to this: If one feels that normally a slight excess of sodium is present in the body then our fluid prescription should include a small amount of sodium,

a gram or two, to maintain this excess.

DR. LUKENS: In connection with pulmonary congestion from too much fluid or sodium, I have seen one or two patients in diabetic coma who were in mild congestive failure. I was impressed with the fact that the first liter or two of fluid given to restore them was just as well absorbed as it would be in a patient without any congestive failure. But beyond that point I am certain that all of us would move carefully in treating such a patient. Accept Dr. Danowski's criterion of so many liters of placement needed but move toward it much more slowly. However, the initial replacement can be given with amazing confidence.

MODERATOR HOWARD: I have personally learned a lot from this discussion. It all boils down to the fact that successful treatment of diabetic acidosis depends on a good physiologic understanding of what has gone wrong and a modicum of common sense.

The Care of the Chronically Sick

Those who care for the chronically sick find that they are concerned not only with the disease, but increasingly with the patient and his disability, with the members of the patient's family, and with the community to which the patient and his family belong. The physician learns that he will need help from the members of the patient's family and from the many health, welfare, and social agencies in the community which exist to serve him in the care of his patient. In chronic illness there are likely to be more serious dislocations of family relationships in their economic and financial aspects. In chronic illness more than in acute illness the physician needs the skills of other members of the health team including the social case worker, rehabilitation experts, physiotherapists, and visiting nurses. It is through chronic illness that one understands why the family has been defined as an autocracy ruled by its sickest member. Care of the chronically ill demands of the physician skills to provide constant and open communication between the patient, the nurse, and himself and with the members of the patient's family. The physician will not only gain inestimably in his understanding of his patient from the different perceptions of others who care for the patient. He also plays an important and indispensable role in fostering and maintaining the morale of the patient and his family. Inevitable human emotions, fear, perplexity, anger, shame and guilt are experienced not only by the patient but by the members of his family. It is important that the physician have some basic understanding of the psychology of chronic illness, of prolonged convalescence and disability so that his mind can be free so far as possible from enslaving emotions in order that he can deal clearly and intelligently with the emotional problems of those whom he is attempting to help.

John Romano, M.D., from an editorial, "Those Who Care for the Sick," *Journal of Chronic Diseases 1*:697, June 1955.

Prevention of Hypoglycemia During the Induction of Alloxan Diabetes

The Use of Glucose and Antihyaluronidase subcutaneously in the Rabbit

Anna R. Spiegelman, M.D., and Marcel Tuchman, M.D.,† New York*

Hypoglycemia presents a serious problem during the induction of alloxan diabetes in the rabbit.[1] Diabetogenic doses of alloxan usually result in an initial hyperglycemia which is soon followed by severe hypoglycemia. The hypoglycemic phase may last for six to eight hours and be severe enough to cause death unless treated promptly. Inasmuch as hyaluronidase enhances the spreading of exogenous or endogenous elements through mesenchymal tissue[2] and thereby speeds absorption, a preparation of antihyaluronidase might be expected to delay and prolong absorption.

Experimental: Immediately after the diabetogenic dose of alloxan (200 mg. per kg. of body weight) was given to 3-to-4-month old rabbits of Dutch a.c. strain, 200 cc. of 5 per cent solution of glucose in water with 100 mg. of antihyaluronidase‡ added was injected subcutaneously. Twelve hours after injection, the subcutaneous mass produced by this solution was still palpable, although smaller. It seemed to be absorbed completely within twenty-four hours.

Results: The first three animals so treated became diabetic. On these, blood sugar determinations were not made at frequent intervals. Nevertheless, there was no evidence of hypoglycemia at any time. Three animals treated subsequently were studied more closely. Blood sugar determinations were made 2 hours, 4 hours, 6 hours, 8 hours and 24 hours after the administration of alloxan and glucose. The blood sugar values (representing true glucose) are presented in the following table. The results suggest that the delayed absorption of glucose provided constant feeding to the animal, thereby preventing hypoglycemia.

TABLE 1

	Blood sugar mg. per 100 cc.		
Rabbit	M*	N	O
Fasting	110	100	115
Alloxan and glucose			
2 hours	510	390	430
4 hours	390	415	400
6 hours	375	415	240
8 hours	105	85	95
24 hours	105	55	220
28 hours		70	240
30 hours		70	275
96 hours		335	

*Rabbit M suffered a fractured spine during the injection of alloxan. Death occurred 26 hours later.

SUMMARY

Antihyaluronidase has been administered subcutaneously along with glucose to delay and prolong its absorption and thus obviate the occurrence of hypoglycemia during the induction of alloxan diabetes in the rabbit. Observations showing successful results are reported.

SUMMÀRIO IN INTERLINGUA

Prevention de Hypoglycemia durante le Induction de Diabete per Alloxano: Le Uso Subcutanee de Glucosa e Antihyaluronidase in Conilios

Antihyaluronidase esseva administrate subcutaneemente insimul con glucosa como retardator e prolongator del processo absorptive pro obviar le occurrentia de hypoglycemia durante le induction de diabete per alloxano in conilios. Es reportate observationes demonstrante le successo del experimento.

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‡Antihyaluronidase (SC 4523) was supplied by Dr. Robert L. Craig of G. D. Searle and Company.

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The Micro-angiopathy in Diabetes Mellitus

A Concept regarding the Mechanism of its Origin

Jørn Ditzel, M.D., and Gösta Rooth, M.D.,† Boston*

Our knowledge of the various causative factors and the mechanism which leads to the generalized micro-angiopathy (retinopathy, intercapillary glomerulosclerosis, and probably neuropathy) in diabetes mellitus is at present insufficient, and a better understanding of this problem is urgent.

Recent research in the field of microbiology of the circulation and in the study of the pathogenesis of retrolental fibroplasia has emphasized the importance of vasomotor reactions in the smaller blood vessels in response to variations in oxygen and carbon dioxide tensions in blood and tissues. The similarities in the clinical pictures and in the patho-anatomic changes between diabetic retinopathy and retrolental fibroplasia are evident. In both conditions the main changes in the retina are vascular in origin and are characterized by engorged and tortuous veins, hemorrhages, and exudates. In some cases of both retrolental fibroplasia and diabetic retinopathy there appear new formation of vessels, vitreous clouding, opacities, and proliferation of connective tissue into the vitreous body. The capillary micro-aneurysms which are the characteristic lesion in diabetic retinopathy have not been demonstrated in the retina of infants with retrolental fibroplasia. This might be explained by the fact that the basement membrane, which is necessary for the formation of the retinal capillary micro-aneurysms, is not developed in the newborn infant.[1] Not only are the above structural similarities present, but the progression of the lesions from mild into severe stages follows the same pathways in both conditions.

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Although not all the details in the mechanism of the production of retrolental fibroplasia are yet known, extensive clinical[2-4] and experimental[5-7] investigations have shown that the most important causative factor is the high concentration of oxygen formerly administered to premature infants placed in incubators. The increase in oxygen tension in the arterial blood of newborn hypoxic infants placed in 40 per cent oxygen is tenfold.[8] Ophthalmoscopic observations have demonstrated that the retinal vessels constrict if the oxygen tension in the circulating blood is increased and that vasodilatation occurs if the oxygen tension is lowered. The same vasomotor reactions to variations in the oxygen tension have been observed in the skin of newborn infants and are known to occur in the smaller vessels of the brain.[9] Identical vasomotor reactions, although in the reverse direction, are caused by variations in the carbon dioxide tension in the circulating blood; that is, an increase in carbon dioxide tension causes a vasodilatation and a decrease in carbon dioxide tension causes a vasoconstriction.[10] In addition, low oxygen tension not only determines the caliber of the retinal vessels but is also the only known incitement for new formation of small vessels.[5]

The vasomotor reactions in the smaller blood vessels (arterioles, capillaries, venules) in response to the variations in oxygen and carbon dioxide tension are not confined to the newborn infant but occur in adult nondiabetic as well as diabetic individuals.[11-14]

In diabetes mellitus the reactions of the smaller blood vessels in the bulbar conjunctiva have been intensively investigated at this laboratory[15-18] with Knisely's technic.[19] In diabetic individuals there were observed pathophysiologic responses of the smaller blood vessels similar to those in subjects exposed to varying oxygen or carbon dioxide concentrations. Two main pattern deviations, which varied quantitatively from time to time, could be recognized in the diabetics. In the vast majority of cases Vascular Pattern Change 1 was found. This is characterized by a slight constriction of the terminal arterioles and a marked loss of tone in the venous part of the peripheral vascular bed, accompanied by aggregation of the blood cells, a decreased rate of blood flow, and ab-

normal permeability. In some cases Vascular Pattern Change 2 was observed. This is characterized by an increase in the vascular tone, since both the arterioles and the venules are tightly constricted and many of the capillaries are completely closed. By serial observations and by statistical evaluation of single observations in diabetic children[17, 18] causative links were demonstrated between the reversible response changes and the irreversible degenerative changes in the bulbar conjunctiva. It therefore appears that the pathophysiologic vasomotor responses over a period of years lead to the permanent clinical micro-angiopathy in diabetes.

In well controlled diabetic persons there is evidence that the partial tension of carbon dioxide (pCO_2) varies concomitantly with insulin administration.[20-22] In the first hours after the administration of insulin the pCO_2 increases and then decreases slowly as the insulin action disappears. More marked changes in pCO_2 occur in acidosis. In this condition the expected sequence of vasomotor reactions was observed; that is, when the pCO_2 was reduced, Vascular Pattern Change 2 was found, and as the patients improved and their pCO_2 increased, the caliber of the vessels reversed through Vascular Pattern Change 1 (dilatation), to resume finally the same condition as they had prior to acidosis.[23] It is a general clinical impression that diabetics who frequently become acidotic are more prone to develop early and severe diabetic micro-angiopathy than are well regulated diabetic patients.

Far less is known about the variations in oxygen tension in diabetics. There is some evidence that oxygen is better utilized at high glucose levels, which suggests the possibility that the oxygen tension in the tissues of diabetics may also change concomitantly with glucose levels and insulin administration.[24] In this regard it might be mentioned that prolonged hyperglycemia has been suggested as a cause of venous distension in the retina.[25] In the diabetics the vasomotor reactions due to changes in oxygen and carbon dioxide tensions in the blood may be aggravated because of the strong tendency of the circulating red cells to aggregate in these patients. These aggregates, which can periodically plug the terminal arterioles or cause the formation of microthromboses in the smaller venules and in the venous part of the capillaries, contribute to the development of stagnant hypoxia.[15]

SUMMARY

It has been pointed out that a comparison between the vascular changes in retrolental fibroplasia and in diabetes mellitus suggest a mechanism leading to the micro-angiopathy in diabetes mellitus. The concept of this mechanism is based on the pathophysiologic vasomotor reactions in response to variations in the oxygen and carbon dioxide tensions over a period of years.

SUMMARIO IN INTERLINGUA

Le Micro-Angiopathia in Diabete Mellite: Un Nove Concepto Relative al Mechanismo de su Origine

Es signalate que le comparation del alterationes vascular in fibroplasia retrolental con le alterationes vascular in diabete mellite suggere le existentia de un mechanismo que effectua le micro-angiopathia de diabete mellite. Le concepto de iste mechanismo es basate super le pathophysiologic reactiones vasomotor a variationes observabile in le curso de plure annos in le tensiones de oxygeno e dioxydo de carbon.

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The Basis for the Satisfaction Derived from Eating

Man eats in order to feel satisfied. He thinks little about the nutritive value of his food, in the selection of which the main question, unconsciously asked, is: "Is this food satisfying?"

Several factors no doubt combine to give this sense of satiety; chief among them is the physiologic activity of the digestive tract. Lack of food, with the accompanying rhythmic gastric contractions, gives rise to the sensation which is interpreted as hunger—even to hunger pains; while a full stomach, physiologically active, with its muscular and secretory functions fully unfolded, produces the opposite feeling, a sense of satisfaction. The food which gives this sensation in highest degree and longest is that which remains longest in the stomach and small intestine and demands of these organs greatest functional activity. Foods as a rule show the same behavior in this respect in both the stomach and the intestine, for those foods which remain longest in the stomach and call forth the greatest secretion of hydrochloric acid also remain longest in the intestine. For such foods a greater length of time is required in the intestine for the neutralization of the acid which comes from the stomach and therefore a longer time for the completion of digestion. The satiety value of an article of diet can therefore be measured in two ways: (a) by the length of time the food remains in the stomach and (b) by the amount of gastric juice stimulated by it.

From the book *Nutrition and Diet in Health and Disease* by James S. McLester, M.D., and William J. Darby, M.D., Ph.D. Philadelphia, W. B. Saunders Co., 1952, 6th ed., p. 130.

The Digestibility of Fats

Contrary to the lay opinion, fats are not poorly digested as is indicated by the high coefficient of digestibility of fat. Langworthy, in his studies on animals fats, found that the coefficients of digestibility range from 97 per cent for butter to 88 per cent for mutton fat. He observed that the presence of considerable quantities of fat in the diet (about 100 gm.) did not alter the digestibility of the other foodstuffs. For instance, the digestibility of the carbohydrate quota, independent of the kind of fat and of its amount, remained practically the same, about 97 per cent. The average coefficient of available energy from all sources was approximately the same (91 to 93 per cent), no matter what the kind of fat, or within the limits of the experiment, its amount. He concluded that fats do not appreciably influence the digestibility of the other food.

The interesting observation was made that beef fat differed from the other fats tested (lard, mutton fat, and butter) in that it often produced diarrhea when as much as 140 gm. were taken, whereas the other fats taken in like amounts did not show such a tendency.

These studies by Langworthy led to the generally accepted conclusion that fats of low melting point are more completely assimilated than those which are fluid only at higher temperature. A similar conclusion was reached in the studies of Matill and Higgins, but these authors, like Holt and his associates, pointed out that other factors also are of influence. They state that the type of glyceride in which this fat occurs in the food is an equally important factor in determining its digestibility.

From the book *Nutrition and Diet in Health and Disease* by James S. McLester, M.D., and William J. Darby, M.D., Ph.D. Philadelphia, W. B. Saunders Co., 1952, 6th ed., pp. 135-36.

ABSTRACTS

Alexander, Frank (*Dept. of Veterinary Pharmacol., Univ. of Edinburgh, Edinburgh, Scotland*): FACTORS AFFECTING THE BLOOD SUGAR CONCENTRATION IN HORSES. Quart. J. Exper. Physiol. 40:24-31, January 1955.

In a survey of 141 horses, Holt and Reynolds found the range for blood sugar between 78 and 370 mg. per 100 ml.; and, in a similar study, Stewart and Holman gave a range of 54 to 95 mg. per 100 ml. However, both these studies were concerned with single observations on a large number of animals and gave no information about the variation within a single animal. The experiments described here show the fluctuation in the blood sugar concentration in individual animals over periods of up to three years. Most of the values obtained in the eight animals under observation were within the range of Stewart and Holman's results, and it is difficult to accept those given by Holt and Reynolds as applying to healthy horses.

Orally administered glucose caused hyperglycemia associated with the presence of a large concentration of glucose in the ileum. Within three hours after the animals were fed hay, a yeast-fermentable reducing substance appeared in the ileal contents in concentrations equivalent to 40 to 90 mg. of glucose per 100 ml. Withholding food usually caused a fall in blood sugar concentration during the first 48 hours and, thereafter, a small rise. The horse, in contrast to the ruminant, is able to digest and absorb soluble carbohydrates without subjecting them to fermentation.

Aun, Yeoh Seang: STEATORRHOEA AND DIABETES MELLITUS ASSOCIATED WITH PANCREATIC CALCULI. Proc. Alumni A. Malaya 7:232-33, September 1954.

Pancreatic insufficiency may appear during the later stages of chronic pancreatitis and diabetes mellitus. The latter complication is more often seen in the interacinar type of diffuse fibrosis involving the parenchyma of the pancreas rather than in the interlobular type.

Ayer, A. Ananthanarayana (*Inst. of Anat., Stanley Med. Coll., Madras, India*): A PRELIMINARY NOTE ON A NEW METHOD OF ADMINISTRATION OF INSULIN BY INHALATION OF THE NEBULIZED SOLUTION. Antiseptic 51:1161-67, October 1954.

On the basis of clinical trial, it is claimed that effective absorption of insulin of therapeutic value takes place through the whole respiratory epithelium through inhalation of the nebulized mist of an insulin solution. The nebulizer used is a midget inhaler. The technic of inhalation consists of three phases: (1) inspiration through the less congested half of the nasal cavity when the nebulized mist is raised by frequent compression and release of the inhaler bulb, (2) holding the breath with the nostrils closed for 4 or 5 seconds, and (3) slow expiration through the other nostril. The breathing is normalized in a few minutes, and the inhalation is repeated until the prescribed dose contained in the reservoir is nebulized and deposited as a thin film on the epithelium of the entire respiratory tract.

Bauman, Everett O.; Grunt, Louis; Brandman, Otto; and Weiss, Selma (*Martland Med. Center, Newark, N. J., Genl. Hosp., East Orange, N. J., and St. Michael's Hosp., Newark, N. J.*): DIABETIC NEPHROPATHY. J. M. Soc. New Jersey 52:55-60, February 1955.

An outline of some of the features of diabetic nephropathies has been presented and an analysis made of 32 cases of diabetic nephropathies compared with a control series of 33 cases of diabetes of an average duration of 23 years without evidence of nephropathy. Sixteen of the 33 control cases were deemed "under poor control," as judged by erratic carbohydrate balance and/or one or more incidents of acidosis. It was, therefore, difficult to understand why they remained free of nephropathy and practically free of vascular degenerative processes. It is suggested that the emotional background of the patient may play a large part in the development of vascular and glomerular complications.

Becker, W. H. (*Chirurgische Klinik der Justus-Liebig-Hochschule, Giessen, Germany*): AN UNTRACEABLE ISLAND-CELL ADENOMA TREATED BY SUBTOTAL PANCREATECTOMY. Deutsche med. Wchnschr. 80:496-97, April 1955.

Subtotal resection of the pancreas resulted in complete freedom from symptoms in a patient suffering from an islet cell adenoma near the head of the pancreas. A critical evaluation of the operative procedures for islet cell adenoma showed that, in these cases, the postoperative hyperglycemia is in inverse proportion to the extent of the resection. Subtotal pancreatectomy is, therefore, chosen in preference to any other form of partial resection or to enucleation of the adenoma. (German)

Beloff-Chain, Anne; Catanzaro, R.; Chain, E. B.; Masi, I.; Pocchiari, F.; and Rossi, C. (*Laboratorio de Chimica Biologica, Istituto Superiore de Sanita, Rome, Italy*):

THE INFLUENCE OF INSULIN ON CARBOHYDRATE METABOLISM IN THE ISOLATED DIAPHRAGM MUSCLE OF NORMAL AND ALLOXAN DIABETIC RATS. Proc. Roy. Soc., London, S. B. *143*:481-503, May 17, 1955.

The fate of uniformly labelled C^{14} glucose in the isolated diaphragm muscle of normal and alloxan diabetic rats has been studied by a quantitative application of the radio paper-chromatographic technic. No significant differences were observed in the metabolism of glucose by muscle from normal and diabetic rats. About 80 per cent of the glucose metabolized by the muscle in the absence and presence of insulin has been accounted for. The extra glucose disappearing from the incubation medium in the presence of insulin was found to be incorporated in oligo- and polysaccharides; the percentage of glucose converted into the other main metabolites (i.e., lactic acid, hexose phosphate esters, and carbon dioxide) was shown to be unchanged or decreased by insulin. Insulin markedly accelerated the synthesis of oligo- and polysaccharides. Under anaerobic conditions, the total glucose metabolism was very reduced, and the greater part of the glucose disappearing from the medium was recovered as free glucose in the tissues. Very little radioactive lactic acid was formed under anaerobic conditions, except when the muscle was incubated with C^{14} glucose first aerobically and then anaerobically; under these conditions there was a considerable accumulation of radioactive lactic acid.

Bertram, Ferdinand (*Medizinische Klinik des Allgemeinen Krankenhauses Hamburg-Barmbeck, Germany*): EXPERIENCES WITH LONG INSULIN "HOECHST." Deutsche med. Wchnschr. *80*:220-21, Feb. 11, 1955.

The properties of and indications for slowly acting Insulin "Hoechst" are discussed.

Particular emphasis is placed on the fact that it is suitable only for patients with stable metabolism and those who may be relied upon to keep their diets.

Considering the experiences described in detail, Long Insulin represents considerable progress in diabetes therapy. (German)

Björklund, S.-I.; and Jensen, C. C. (*Flensburg Children's Hosp. and Dept. of Gynecology, Genl. Hosp., Malmo, Sweden*): INFANTS OF DIABETIC MOTHERS WITH SPECIAL REFERENCE TO NEONATAL ADRENOCORTICAL FUNCTION AS ASSESSED BY URINARY EXCRETION OF 17-KETOSTEROIDS. Acta endocrinol. *18*:133-40, February 1955.

The authors have investigated the adrenocortical function in newborn infants of diabetic mothers with regard to the excretion of 17-ketosteroids. A study was made of seven infants delivered by cesarean section after a pregnancy of 34 to 37 weeks .In six cases, the values for the urinary 17-ketosteroids were considerably higher during the first four days than in 19 spontaneously delivered babies of nondiabetic mothers. The cause of the high values, which were regarded as related to an increased adrenocortical function, is discussed.

Dana, George W.; and Zubrod, Charles G. (*Depts. of Med. and Pharmacol. and Experimental Therapeutics, Johns Hopkins Univ. Sch. of Med. and Johns Hopkins Hosp., Baltimore, Md.*): THE CLINICAL FEATURES ASSOCIATED WITH KIMMELSTEIL-WILSON LESIONS. Bull. Johns Hopkins Hosp. *95*:338-45, December 1954.

A report has been made of the clinical characteristics of 45 patients shown to have Kimmelsteil-Wilson nodules in the renal glomeruli at autopsy. These clinical features have been contrasted with those of 133 diabetic patients who were proved at autopsy not to have Kimmelsteil-Wilson nodules. The data on duration of diabetes and the age of the patient at onset bring out no remarkable differences between the Kimmelsteil-Wilson group and the controls, except that those patients who die after less than five years of diabetes rarely exhibit nodules. It is also noted that the development of nodules is not a simple function of the duration of diabetes, since 29 patients had diabetes for 11 years or longer but had no glomerular nodules. Diabetic retinitis was present in 35 of the 45 patients with Kimmelsteil-Wilson lesions and in only 12 of the 133 control patients. The combination of retinitis and peripheral edema was a reliable diagnostic point in favor of the presence of glomerular nodules. The classical triad of hypertension, albuminuria, and edema occurred in less than half of the patients with Kimmelsteil-Wilson nodules but, when present, was strong evidence in favor of the diagnosis of Kimmelsteil-Wilson nodulation. The coexistence of arteriosclerosis and arteriolosclerosis of the kidneys with Kimmelsteil-Wilson nodulation occurs frequently. Six patients with the most marked nodulation of the glomeruli had, during life, severe edema, hypertension, proteinuria, and uremia. In addition, each had extensive arteriosclerotic and arteriolosclerotic nephritis. These latter diseases in pure form are not generally associated with marked edema in the absence of cardiac failure. This study points out that patients with Kimmelsteil-Wilson nodulation often develop edema not explicable on the basis of cardiac failure. Dilatations of the glomerular capillaries similar in appearance to the retinal aneurysms have been noted in 11 patients with Kimmelsteil-Wilson nodules.

Donaldson, Kenneth O.; Hall, H. Eugene; Hawthorne, Edward W.; and Marshall, Lawrence M. (*Depts. of Biochem. and Physiol., Howard Univ. Sch. of Med., Washington, D. C.*): CARBON DIOXIDE UTILIZATION BY RABBIT LIVER. Science *120*:844-45, Nov. 19, 1954.

During an investigation of labeled carbon dioxide fixation into the organic acids of liver homogenates, the authors observed that such incorporation of the isotope in the liver of the rabbit differed from that of other species examined. Fixation was as great or greater into a compound insoluble in the solvent that readily dissolves such acids as succinic, fumaric, and malic. Further chromatographic study indicated a compound related to glycolaldehyde and suggested a metabolic pathway whereby the carbon was first fixed into a hexose, the precursor of sedoheptulose, which later cleaved between carbons 2 and 3 to produce the labeled glycolaldehyde.

Drury, Douglas R.; Wick, Arne N.; and Morita, Toshiko N. (*Scripps Metabolic Clin., La Jolla, and Dept. of Physiol., Sch. of Med., Univ. of Southern Calif., Los Angeles, Calif.*): METABOLISM OF LACTIC ACID IN EXTRAHEPATIC TISSUES. Am. J. Physiol. *180*:345-49, February 1955.

Eviscerated animals oxidize large amounts of the natural form of lactic acid. This is presumably due to the high plasma concentration of lactic acid uniformly found in this preparation. Evidence is presented which indicates that there is a high turnover rate of lactate in the eviscerated animal.

The findings suggest that the relatively low rate of glucose oxidation observed in the extrahepatic tissues after insulin administration is due to the preferential use of lactate as a fuel.

The unnatural form of lactate [D (+)] is oxidized very sparingly by these tissues.

Duff, G. Lyman; Brechin, Doris J. H.; and Finkelstein, W. E. (*Dept. of Path., Pathological Inst., McGill Univ., Montreal, Canada*): THE EFFECT OF ALLOXAN DIABETES ON EXPERIMENTAL CHOLESTEROL ATHEROSCLEROSIS IN THE RABBIT. J. Exper. Med. *100*:371-80, Oct. 1, 1954.

Studies were made to ascertain whether the previously demonstrated inhibition of the development of experimental aortic atherosclerosis in alloxan-diabetic rabbits fed cholesterol was due to the injection of alloxan per se or to the existence of the diabetic state produced by alloxan. It was observed that, by treating the diabetic state with insulin, the diabetic state could be ameliorated and the inhibitory effect obviated. It was therefore concluded by the authors that the inhibitory effect was not due to the injection of alloxan per se but that it was associated with one or more factors that characterize the alloxan-diabetic state in the rabbit and are reversible by insulin therapy.

In the course of the experiment, it was demonstrated that the inhibitory effect was apparent in cholesterol-fed diabetic rabbits whether or not their diet was supplemented with vegetable oil. The previously reported metabolic abnormalities of the diabetic animals were confirmed. It was also established that suitable treatment of the cholesterol-fed diabetic animals with insulin would bring all the metabolic aberrations, including those of the serum lipids, into reasonably close correspondence with those observed in nondiabetic rabbits fed cholesterol.

Editorial (*Buenos Aires, Argentina*): DIABETES IN INFANTS. Orientación Médica *4*:457, May 27, 1955.

Diabetes is exceptional in infants under one year of age and even more exceptional in infants between one and two and a half years of age. Diabetes in the newborn is exceptional and very difficult to diagnose, because of the variability of the blood sugar in this period of life. There are no characteristic clinical findings with the exception of loss of weight, which could be rapid regardless of a normal appetite. Glycosuria, acetonuria, hyperglycemia (with the blood sugar 500 to 900 mg. per 100 cc.), and decrease in the carbon dioxide combining power are commonly present. If the treatment is not adequate, diabetes will rapidly progress to death. Diabetes occurring during the first year of life is manifested by clinical symptoms such as polydipsia, polyuria, anorexia, loss of weight, vomiting, constipation, and, sometimes, cataracts. Diabetes occurring between one and two and a half years of age frequently develops during an infectious disease or following trauma. The onset is always slow, and polydipsia and polyuria are quite noticeable, as are anorexia and loss of weight. Treatment of diabetes under these circumstances is confined to the use of soluble insulin at the onset of treatment and combination with long-acting preparations afterwards. (Spanish)

Editorial (*Buenos Aires, Argentina*): JOSLIN'S OPINION OF THE IMPORTANCE OF CONTROL IN DIABETES. Día méd. *27*:849-52, May 12, 1955 (Spanish translation of Editorial in J.A.M.A. *156*:1584-85, Dec. 25, 1954):

The chief goal of the treatment of diabetes is not only the increase in life expectancy but also the restoration of the insulin-producing mechanism to normal or at least the avoidance of a functional derangement. This is attained mainly through a rigid control of the disease by diet and insulin. (Spanish)

Fischberg, David: INSULIN RESISTANCE ASSOCIATED WITH CANCER OF THE KIDNEY AND INSULIN ALLERGY. Día méd. 27:686-91, Apr. 25, 1955.

Insulin resistance of one year's duration developed in a diabetic patient who had had nephrectomy because of cancer of the kidney. Two months after the appearance of insulin resistance, allergy to insulin was disclosed. The maximal daily insulin requirement was 4,870 units, and the maximal average dosage in four months was 3,000 units. In the following months, the insulin requirement progressively decreased to 1,000 units daily, then 800 units. Later, when the patient became cachectic, the insulin requirement dropped to daily dosages used before the occurrence of malignancy. (Spanish)

Fischer, Franz: PROBLEMS OF DIABETIC RETINOPATHY. Klin. Monatsbl. Augenh. *125*:666-72, 1954 (Abstracted from Am. J. Ophth. 39:614, April 1955).

The author discusses the work of Loewenstein and Ballantyne, Friedenwald, and Becker.

Foglia, Virgilio G. (*Buenos Aires, Argentina*): PREDIABETES. Semana méd., 60th Anniversary Commemorative Issue, 30-34, 1954.

Ablation of 95 per cent of the pancreas in the white rat produces a diabetic picture of slow onset which is different from the other types of experimental diabetes. In the course of its development, the following stages are present: (1) Inapparent diabetes, which lasts approximately a month, extending from the operation to the appearance of alimentary glycosuria. There are no clinical signs of diabetes in this state. (2) Incipient diabetes, which extends from the alimentary glycosuria to the fasting hyperglycemia. This period lasts from one to two months, and it records the onset of the clinical signs of the disease, such as polyphagia, polydipsia, glycosuria, loss of weight, etc. Histologic examination during these two stages shows reversible changes in the beta cells. (3) The confirmed diabetes, which shows the full-blown clinical picture of the disease including some degenerative vascular lesions. It lasts from 7 to 11 months, up to the death of the animal in cachexia. Irreversible lesions of the beta cells are found in this stage. A high calorie diet, as well as a high fat diet, seems to shorten the duration of these stages. The administration of male hormones seems to produce the same result, unlike the female hormones, which prolong the duration of these stages. From these observations, it is concluded that estrogens have a protective role upon the appearance of diabetes. Thyroid administration seems to shorten the duration of these stages, unlike thyroidectomy or administration of antithyroid medication, which prolongs the duration. (Spanish)

Folk, Martha Rubin (*Dept. of Ophth., Mount Sinai Hosp. and Chicago Med. Sch., Chicago*): LIPOLIQUID IN TREATMENT OF HEMORRHAGIC DIABETIC RETINOPATHY. A.M.A. Arch. Ophth. *53*:93, January 1955.

Fifty patients with diabetic retinopathy were treated with Lipoliquid, containing choline, inositol, and vitamin B_{12}. When associated with retinitis proliferans, treatment was completely unsuccessful. About half of the patients without proliferation showed no progression, and the remainder only slight progression. This group of patients frequently maintained their visual acuity for a long period of time; however, the development of retinitis proliferans in two cases and of recurrent hemorrhages in all cases suggests that Lipoliquid is of very limited value in the treatment of hemorrhagic diabetic retinopathy.

Gray, Doris E.; and De Luca, H. A. (*Dept. of Physiol., Univ. of Hong Kong, Hong Kong, China, and Univ. of Western Ontario, London, Ontario, Canada*): EFFECT OF VITAMIN E ON CARBOHYDRATE METABOLISM OF RAT DIAPHRAGM. Canad. J. Biochem. & Physiol. *32*:491-97, September 1954.

A study was made of the carbohydrate metabolism of diaphragm isolated from rats maintained on diets containing deficient, sufficient, or excessive quantities of vitamin E. No effect was observed on glycogen formation, glucose uptake, lactic-acid accumulation, or oxygen consumption as a result of differences in vitamin E intake. Rats receiving a diet deficient in vitamin E may have a slightly decreased capacity to form pyruvic acid or a slightly increased ability to utilize it. The addition of insulin to the incubation medium counteracted this effect of the vitamin lack.

Guimarães, José Ricardo Alves (*São Paulo, Brazil*): STUDIES ON DIABETES. IV. Rev. méd. brasil. *38*:49-56, February 1955.

Twenty-seven patients with mild diabetes were treated with diet and insulin. Twenty patients (74 per cent) were considered permanently cured, and two patients (7 per cent) were considered perhaps permanently cured. One patient was regarded as dubiously cured, and four patients were listed as failures. A patient was considered to be permanently cured when normoglycemia and aglycosuria were present for a period of two years after discontinuance of insulin and diet. The patients were, in general, obese and sedentary. Usually an emotional stress preceded the onset of diabetes. A low-calorie diet was used to obtain weight reduction; mercurial diuretics were given during the first few days in order to enhance the loss of weight. An iodinated casein with the same biological effects of thyroxin was used with the idea that it might inhibit the pituitary secretion of diabeto-

genic hormones. (Portuguese)

Heupke, W.; and Meyerheim, G.: COMPLICATIONS AND PROGNOSIS IN DIABETES MELLITUS. München. med. Wchnschr. *42*:693-96, March 11, 1955 (Abstract in Prensa méd. argent. *42*:693-96, March 11, 1955).

In 1940, the incidence of diabetes was 0.2 per cent in Germany; at present, this figure has increased to 0.6 per cent. Although the prognosis in diabetes has improved considerably in the last few years, the life expectancy of the diabetic patient is still below that of the normal individual. This is attributable to degenerative complications which develop in association with the metabolic disturbances in diabetes. Obesity favors the appearance of diabetes and makes the diabetes difficult to control. Arteriosclerosis seems to be related more to disturbances in fat metabolism than to hyperglycemia. This degenerative process affects mainly the coronary vessels, peripheral arteries, retinal arteries, and renal arteries. Arteriosclerosis is responsible for the high mortality rate in diabetes (60 per cent). Another factor affecting the prognosis in diabetes is the higher incidence in this group of pulmonary tuberculosis and infectious processes. (Spanish)

Hill, R.; Baker, N.; and Chaikoff, I. L. (*Dept. of Physiol., Univ. of Calif. Sch. of Med., Berkeley, Calif.*): ALTERED METABOLIC PATTERNS INDUCED IN THE NORMAL RAT BY FEEDING AN ADEQUATE DIET CONTAINING FRUCTOSE AS SOLE CARBOHYDRATE. J. Biol. Chem. *209*:705-16, August 1954.

The response of plasma glucose to orally administered glucose (glucose tolerance test) was compared in three groups of normal rats, i.e., those (1) fed for three days an adequate diet containing 58 per cent glucose as sole carbohydrate, (2) fed for the same period a diet containing 58 per cent fructose, and those (3) fasted for 96 hours. An impaired capacity to utilize glucose was observed in the fructose-fed rats. The glucose tolerance curves in these rats resembled those observed in the fasted rats.

The evidence obtained from studies of the utilization by liver, kidney, and brain of compounds labeled with radioactive carbon (C^{14}) and of glucose uptake by diaphragm suggested to the authors that the decrease in glucose tolerance observed in the fructose-fed rat was the result of an impaired liver glucokinase activity. Insulin administrations, even for as long as three days before the fructose-fed rats were sacrificed, failed to augment the ability of their livers to oxidize glucose to carbon dioxide.

These findings are considered as a manifestation of enzymatic adaptation to diet.

Hirata, Yukimasa (*Faculty of Med., Kyushu Univ., Fukuoka, Japan*): STUDIES ON EXPERIMENTAL DIABETES. Kyushu Mem. Med. Sci. *5*:95-101, September 1954.

After the administration of alloxan, serum potassium concentration of rabbits increased with the initial hyperglycemia and decreased in the hypoglycemic phase. It was experimentally proved in rats that the sodium thiolactic acid prevented the development of alloxan diabetes. The reaction of dithizone with zinc was prevented by sodium thiolactic acid or BAL but not by sodium thiosulfate. Administration of sodium thiolactic acid or BAL before the injection of dithizone prevented the development of dithizone diabetes; however, sodium thiosulfate had no such preventive action.

Huggett, Arthur St. George (*Dept. of Physiol., St. Mary's Hosp. Med. Sch., Univ. of London, London, England*): GROWTH, PREGNANCY, AND CARBOHYDRATE METABOLISM. Am. J. Obst. & Gynec. *69*:1103-26, May 1955.

Comparative rates of fetal growth in relation to umbilical blood flow and the peculiarities of fetal growth which bear upon problems of carbohydrate metabolism in the fetus and pregnancy are discussed. It is stated that the glycogen of the placenta has certain physiological characteristics which distinguish it from liver glycogen; for example, it is independent of the content of sugar or endocrines in the blood. Placental glycogen can be decreased only by toxic doses of thyroxin or insulin. Hoet (Abstracts of Communications, 19th International Physiological Congress, Montreal, 1953, p. 469), has shown that cortisone will increase the quantity of placental glycogen in rabbits.

The amount of glucose and fructose in amniotic fluid and fetal blood of sheep are reviewed. It has been shown that the sheep's placenta forms fructose from glucose and that the fetal blood fructose is dependent on its placental source. Human fetal blood probably has up to 4 to 5 mg. of fructose per 100 cc., but, in contrast to the sheep fetus, glucose is present in much greater proportions. Differences in the production and transfer of glucose and fructose by the placenta into the fetal blood stream are discussed.

Irving, E. M.; and Wang, I. (*Glasgow, Scotland*): THE EFFECT OF THE PREVIOUS DIET ON GLUCOSE TOLERANCE TESTS. Glasgow M.J. *35*:275-78, November 1954 (Abstracted from J.A.M.A. *157*:1052, March 19, 1955).

In many cases, a diet containing 300 gm. of carbohydrate given before a glucose tolerance is far in excess of normal requirements and proves nauseating. The authors investigated to find whether or not the diet containing this amount of carbohydrate was necessary in a person whose diet had been sufficient to maintain

adequate nutrition.

A diet containing 100 gm. of carbohydrate daily was chosen as being probably below the daily consumption of the hospital patient maintaining adequate nutrition. The effect of this diet on the sugar tolerance of 12 normal persons was compared with that of a diet containing 300 gm. of carbohydrate daily. After the low carbohydrate diet, no values were obtained that approximated a diabetic curve, but it was noted that in two cases an "oxyhyperglycemic" curve was obtained. It is concluded that there is no necessity for augmenting the normal diet of an adequately nourished patient before the performance of a glucose tolerance test.

Ishihara, Ichiro; Komori, Yoshitaka; Minamikawa, Yutaka; Iida, Hideo; and Mukai, Takeo (*Res. Inst. of Environmental Med., Nagoya Univ. and 1st Dept. of Internal Med., Nagoya Univ. Sch. of Med., Nagoya, Japan*): INSULIN RESPONSE IN NEUROENDOCRINE DISORDERS. Nagoya J. Med. Sci. *16*:275-86, December 1953.

The responses after the injection of insulin were investigated in the changes of blood sugar and eosinophil counts in neuroendocrine disorders. In adrenocortical insufficiency, the decrease of eosinophils in the circulating blood was insufficient and abnormal in spite of the sensitive decrease of blood sugar. In acromegaly, responses to insulin, epinephrine, and intramuscular corticotropin were all abnormal. However, intravenous corticotropin showed a definite reduction of eosinophils in some cases and not in others. In adiposogenital dystrophy, insulin and intramuscular corticotropin responses were resistant, but normal response occurred to epinephrine. In most cases of pituitary emaciation and one case of dwarfism, there was insulin sensitivity, as shown by the decrease of blood sugar and exaggerated eosinopenia. In one case of emaciation, however, eosinopenia was absent in spite of the marked decrease of blood sugar. Normal insulin response in a case of eunuchoidism became paradoxical during the administration of testosterone propionate. In cases of goiter with hypothyroidism, response to insulin was absent, whereas in a case of goiter with hyperthyroidism, it was normal. In almost all cases of diabetes mellitus, abnormal response to insulin was found. In diabetes insipidus, there were cases in which responses to insulin, epinephrine, and corticotropin were abnormal. These clinical investigations lead us to conclude that insulin-induced eosinopenia is controlled neurally as well as hormonally. It gives a useful guide for the detection of neuroendocrine disorders in which hormone imbalance and disturbances of diencephalopituitary system exist.

Jones, Charles H.; Blachly, Paul H.; and Brookhart, J. M. (*Northern State Hosp., Sedro Woolley, Wash., and Dept. of Physiol., Univ. of Oregon Med. Sch., Portland, Ore.*): THE ANALEPTIC ACTION OF PERIPHERAL ELECTRICAL STIMULATION IN INSULIN COMA. A.M.A. Arch. Neurol. & Psychiat. 73:560-64, May 1955.

Arousal from deep hypoglycemic coma was produced by peripheral electrical stimulation in each of 15 trials on seven patients. No relationship was seen between the duration of stimulation required for arousal and the duration of coma prior to stimulation or the blood glucose level. Two arousals occurred with no significant increase in blood glucose, and one arousal occurred with a marked decrease in blood glucose. Termination of hypoglycemic coma by means of peripheral electrical stimulation is not dependent upon an increase in blood glucose, but is thought to be due to an arousal mediated by the ascending portion of the reticular activating system.

Korngold, Leonhard; and Lipari, Rose (*Sloan-Kettering Inst. for Cancer Res., New York, N. Y.*): IMMUNOCHEMICAL STUDIES OF HUMAN PLASMA BETA LIPOPROTEIN. Science *121*:170-71, Feb. 4, 1955.

The authors report upon low-density beta lipoproteins in human plasmas studied by the agar-diffusion technic devised by O. Ouchterlony.

Kosaka, Kinori; and Kuzuya, Nobusada (*Okinaka Clin., Tokyo Univ., Tokyo, Japan*): THE STAUB-EFFECT IN DIABETIC CONDITIONS AND IN NORMAL RATS. Endocrinologia Japonica *1*:99-107, September 1954.

In all diabetic conditions, even in completely depancreatized dogs, the Staub-effect is recognizable if the interval between two doses of glucose is adequately determined. In normal rats having intact pancreases, the Staub-effect is always negative, even if the time interval is changed in various degrees.

It is not accepted that the Staub-effect is due to an increased secretion of insulin, stimulated by the hyperglycemia after glucose administration, or that it would serve as an index of the islet function.

Lachance, Jean-Paul; and Pagé, Edouard (*Dept. of Physiol. and Nutrition, Faculty of Medicine, Laval University, Quebec, Canada*): THE EFFECT OF INSULIN AND THYROXINE ON THE GLYCOGEN AND ASCORBIC ACID CONTENT OF THE BROWN ADIPOSE TISSUE IN RATS. Rev. canad. biol. *14*:74-88, March 1955.

Prolonged administration of insulin has no effect on the fresh weight and glycogen content of the brown adipose tissue. In rats refed after an eighteen-hour fast and given a concomitant dose of insulin, the brown fat resumes its prefasting weight and shows a large increase in glycogen content. Refeeding alone has a significantly lesser effect. Under the influence of thyroid hormone, hypertrophy of the brown adipose tissue and decrease in depot fat occurs. The hypertrophy corresponds al-

most exclusively to fat deposition, in contrast to the effect of cold. Under experimental conditions, neither thyroxine, insulin, nor the dietary fat level affect the ascorbic acid content of the brown adipose tissue. The lesser concentration sometimes observed is merely a dilution effect following hypertrophy of the tissue. (French)

Lafuente, A. (*Inst. Patología Médica, Madrid, Spain*): JUVENILE DIABETES AND CUSHING'S SYNDROME. Bol. inst. patol. méd. 9:101-06, June 1954.

Two juvenile diabetics have been studied. Diabetes was discovered when patients were 9 and 12 years old, respectively, and their courses were characterized by frequent acidosis and resistance to insulin. After some years of treatment, these two patients developed amenorrhea, followed by localized obesity, lymphocytosis, and increased excretion of 17-ketosteroids in the urine. The general picture was compatible with Cushing's syndrome. It is possible to assume that in the genesis of both conditions—diabetes and Cushing's syndrome—there has been an overfunction of the contra-insular mechanism involving mainly the hypophysis. (Spanish)

Masoro, E. J.; and Abramovitch, Henry (*Dept. of Physiol., Tufts Coll. Med. Sch., Boston, Mass.*): EFFECT OF INSULIN ON ETHANOL METABOLISM. Canad. J. Biochem. & Physiol. 32:465-69, July 1954.

The role of insulin in ethanol metabolism was investigated with the aid of ethanol labeled with radioactive carbon (C^{14}). Surviving kidney and liver slices prepared from insulinized rats oxidized ethanol to carbon dioxide at approximately the same rate as did slices prepared from control rats. The possibility that the beneficial effects noted in the treatment of acute alcohol intoxication with insulin may be the result of an increased synthetic metabolism is discussed.

Mellinkoff, Sherman M.; Boyle, David; Frankland, Marjorie; and Greipel, Margaret (*Dept. of Med., Univ. of Calif. (Los Angeles) Med. Sch. and Wadsworth Veteran's Hosp., Los Angeles*): THE EFFECT OF AMINO ACID ADMINISTRATION UPON THE BLOOD SUGAR CONCENTRATION. Stanford M. Bull. 13:117-24, May 1955.

In 15 normal subjects, the infusion of 250 cc. of 10 per cent amino acids in 45 minutes caused a significant fall in the blood sugar concentration. A similar effect was observed in 10 subjects after the ingestion of the same solution of amino acids. It is suggested that a rise in the blood amino acid concentration may provoke the secretion of insulin.

Moya, Francisco (*Dept. of Biochem., Victoria Genl. Hosp., and Dept. of Med., Dalhousie Univ., Halifax, Nova Scotia, Canada*): MODE OF ACTION OF THE HYPERGLYCEMIC-GLYCOGENOLYTIC FACTOR FROM URINE. Endocrinology 56:312-21, March 1955.

The intravenous administration to rabbits of a urinary extract prepared from normal human urine produces hyperglycemia. The doses employed (1 or 5 mg. per kg. of body weight) correspond to a small fraction of the daily output by normal individuals. Fluoride (0.1 M), which completely inhibits the increased glycogenolysis elicited by glucagon in liver slices, does not completely inhibit the glycogenolytic action of the urinary extract. The extract has been shown to contain urinary amylase. It is tentatively concluded that serum amylase may influence the concentration of hepatic glycogen in physiological or pathological states.

Nichols, Myron M. (*Mast Clin., Midland, Texas*): INSULIN ALLERGY: CASE REPORT, WITH RESPONSE TO BOILED INSULIN. J. Pediat. 46:314-16, March 1955.

The term "insulin allergy" denotes a specifically acquired, altered antigenic response to insulin protein, in contradistinction to insulin sensitivity, which denotes an altered physiologic response. Three types of insulin allergy are usually mentioned: mild local reactions, severe local reactions, and generalized reactions, that is, severe urticaria, angioneurotic edema, circulatory failure, asthma, arthralgia, and gastrointestinal symptoms. In a case of generalized insulin allergy in an eleven-year-old white girl, consisting in generalized edema, urticaria, and a weight gain of 5 pounds, there was a good response to emergency treatment with boiled regular insulin. The patient ultimately was desensitized to insulin, and was able to take commercial NPH insulin.

Ota, Shoshi; and Shibata, Masayuki (*Dept. of Med. Chem., Faculty of Medicine, Kyushu University, Fukuoka, Japan*): STUDIES ON THE MECHANISM FOR SUGAR ABSORPTION BY RABBIT INTESTINE. Kyushu Mem. Med. Sci. 5:107-21, September 1954.

The rate of absorption for different sugars has been found to vary in the following order: galactose, glucose, fructose, ribose, xylose, arabinose. All these sugars, except arabinose, are phosphorylated during absorption in this order: fructose, galactose, glucose, ribose, xylose. The results of the experiments on the effects of 2,4-dinitrophenol, phlorhizin, and an anerobic condition indicate that galactose, glucose, ribose, and xylose are phosphorylated by a phosphorylation system "coupled" intimately with the respiratory process. Phosphates required for sugar phosphorylation were found to be supplied successively by the mucous cells, which always contain a small amount of the substance, and not from any intestinal content or the blood. The phosphorylation of fructose to be absorbed appeared to be caused by some unknown specific process different from those for glucose. Arabinose was found to be absorbed by some

physical processes without being phosphorylated. Monoiodoacetic acid inhibited not only the phosphorylation of sugars but also the widespread phosphate metabolism, which caused severe intestinal damage as a result.

Pagé, Edouard; and Babineau, Louis-Marie (*Dept. de physiol. de la nutrition, Faculté de Méd., Univ. Laval, Quebec, P. Q., Canada*): TISSUE GLYCOGEN AND GLUCOSE ABSORPTION IN RATS ADAPTED TO COLD. Canad. J. Biochem. & Physiol. *32*:395-99, July 1954.

Fasted rats previously fed a high fat ration and adapted to cold maintain their liver glycogen as efficiently as their controls kept at room temperature. On a high carbohydrate diet, fasting liver glycogen is markedly higher in the cold-adapted animals. Glucose absorption rate on the high fat regimen is nearly 70 per cent higher following adaptation to cold.

Patrick, Sydney J. (*Biochem. Div., Physiol. Dept., Univ. Coll. of the West Indies, Jamaica, British West Indies*): EFFECT OF HYPOGLYCIN A ON LIVER GLYCOGEN WITH A METHOD FOR THE STUDY OF CHANGES IN LIVER GLYCOGEN. J. Appl. Physiol. 7:140-42, September 1954.

"Vomiting sickness," a seasonal endemic condition in Jamaica, is related to the ingestion of certain toxic foods. One such food is ackee (Blighia sapida) from which has been isolated two compounds, hypoglycin A and B, which have been shown to cause hypoglycemia in animals.

The author describes a method for the determination of glycogen in samples of liver weighing 1 to 5 mg. The method was applied to the determination of glycogen in samples of human liver obtained by biopsy in cases of vomiting sickness. Very low concentrations of glycogen were observed in these cases. Observations were also made on the changes of liver glycogen in rats dosed with hypoglycin A. The administration of this compound produced a marked fall in liver glycogen followed by a fall in blood glucose to low levels. The concentration of liver glycogen rose minimally or not at all after the administration of glucose to a rat dosed with hypoglycin five hours previously.

Peck, Franklin B.; Alfaro, Raul D.; and Evans, J. G. (*Lilly Labs. of Clin. Invest., Genl. Hosp., Indianapolis, Indiana*): INDICATIONS FOR USE OF VARIOUS INSULINS. Semana méd., 60th Anniversary Commemorative Issue, 92-103, 1954.

Insulin therapy is indicated in (1) all diabetic children, (2) diabetics with complications (infections, surgery, etc.), and (3) patients who demonstrate an inability to maintain nutrition without hyperglycemia and glycosuria. It is obviously possible to treat diabetes by means of any insulin preparation, provided suitable rearrangements of dietary distribution and dosage are made. In studies conducted in several countries abroad, distribution of the diet and the mealtimes were made to conform to local dietary habits, and the total caloric intake of carbohydrate, protein, and fat content were controlled. In 240 patients thus treated, NPH insulin afforded a degree of control which paralleled the observations made in the United States; therefore, there is a perfect adaptability of this new modified insulin to types of diet found in Latin America and in some European countries. (Spanish)

Peden, A. Stewart (*Dept. of Pathol., Univ. of Edinburgh, Edinburgh, Scotland*): ATTEMPTED PREPARATION OF ALLOXAN DIABETIC, HYPOPHYSECTOMIZED, ADRENALECTOMIZED (A.D.H.A.) RATS. Acta endocrinol. *18*:67-80, January 1955.

Four attempts have been made to prepare alloxan diabetic, hypophysectomized rats, originally following in the main the method of Bornstein and subsequently modifying it in the hope of securing more survivors. All these attempts failed to produce a significant number of survivors. It was noted that younger rats of lighter weight do not appear to succumb so readily to the diabetogenic action of alloxan, possibly due to islet regeneration from ductules.

Penhos, J. C.: DIABETOGENIC ACTION OF GLUCAGON. Ciencia e Invest. *10*:365, August 1954.

Cavallero, Malandra, and Galansino treated normal rats with glucagon, cortisone, or the combination of both. In order to determine the role of glucagon in the production of alterations in carbohydrate metabolism, 54 male rats were divided into 3 groups. Fourteen rats were given cortisone (5 mg. per day) subcutaneously, 16 rats were given glucagon (0.5 mg./12 hours) intraperitoneally, and 24 rats were given the combination of cortisone and glucagon in the same dosages. The experiment lasted 20 days, and glucose tolerance and insulin tolerance tests were carried out on the fifteenth day. At the end of the experiment, a drop in body weight was observed in the cortisone-treated rats and the cortisone-glucagon-treated rats, unlike the glucagon-treated animals, which increased in body weight. Glycosuria, which gradually increased up to 50 per cent, was observed in the group treated with combined therapy. Fasting glycemia was greater in the rats treated with the combined therapy than in the other groups. Likewise, a decrease in glucose tolerance was observed in the group on combined therapy. This is explained on the basis of a greater release of glucose from the liver owing to glucagon, and this hyperglycemia would be effective enough to produce a relative insulin insufficiency. (Spanish)

Pinto Nogueira, Ismar; and Coelho, Bento (*Serviço de Obstetrícia do Hospital dos Servidores do Estado, Rio de Janeiro, Brazil*): DIABETES IN PREGNANCY: A CLINICAL CASE. Med. cir. farm. *223*:494-501, November 1954.

Estrogen therapy was started at the twenty-second week of pregnancy in a juvenile diabetic patient. A cesarean operation was performed at the thirty-seventh week, and a normal male child was delivered. This patient previously had a stillbirth and an abortion. The author believes that estrogen has a definite place in the treatment of selected diabetic pregnant women. (Portuguese)

Renold, Albert E.; Hastings, A. Baird; and Nesbett, Frances B. (*Dept. of Bio. Chem., Harvard Med. Sch., Boston, Mass.*): STUDIES ON CARBOHYDRATE METABOLISM IN RAT LIVER SLICES. III. UTILIZATION OF GLUCOSE AND FRUCTOSE FROM NORMAL AND DIABETIC ANIMALS. J. Biol. Chem. *209*:687-96, August 1954.

The authors measured the utilization of glucose and fructose by normal and diabetic rat liver slices in a system designed to preserve a normal intracellular cationic environment. The comparative utilization of glucose and fructose was further used to calculate a maximal and a minimal value for total glucose phosphorylation by the tissues studied. Total glucose phosphorylation by diabetic liver slices was decreased to between one-fourth and one-tenth of normal. In contrast, liver slices from diabetic rats utilized fructose at approximately the normal rate. Of the utilized fructose, however, a greater portion was converted to glucose, a finding in keeping with the previously demonstrated tendency to gluconeogenesis in diabetic liver. Although glycogen synthesis from fructose was much greater than that from glucose in liver slices from diabetic rats, glycogen synthesis from fructose was decreased by at least 75 per cent below the normal values.

Roberts, Harold K. (*110 S. Central, St. Louis, Mo.*): DIABETES MELLITUS: ELECTROLYTE AND FLUID BALANCE DISTURBANCES. Missouri Med. *52*:199-202, March 1955.

Solutions containing the proper amounts of extracellular electrolytes are required, and complicated replacement solutions of glucose and intracellular electrolytes are frequently necessary. Intravenous infusions of potassium should be administered slowly, and only when frequent determinations of the serum potassium can be made and when the clinician understands the possible toxic effects. Some of the repair solutions are discussed, and a few are described in detail.

Scheurlen, Paul Gerhardt (*Medizinische Klinik, Kantonsspital Winterthur, Schweiz*): SERUM PROTEIN CHANGES IN DIABETES MELLITUS. Klin. Wchnschr. *33*:198-205, March 1, 1955.

When no accompanying inflammatory diseases existed, an increase of the $alpha_2$ globulins up to double the normal was observed in cases of diabetes especially during decompensation and during coma. In only 2 out of 22 cases was this increase lacking. Beta globulin was also slightly increased, whereas $alpha_1$ globulin remained unchanged. In most cases, gamma globulin was decreased. The protein also showed decreased values. Hyperproteinemia due to the hemoconcentration was noted. With restitution of the metabolic damage, these changes receded considerably; but even with control of diabetes, a minor dysproteinemia of the kind described could frequently be observed. Inflammatory complications caused a greater $alpha_2$ globulin increase. $Alpha_1$ globulin was then increased also. Frequently, lower or decreased gamma globulin values were found.

The described dysproteinemia is not specific to diabetes alone. It can be assumed that every severe and acute metabolic disorder or electrolytic fluctuation goes hand in hand with serum protein changes. (German)

Selye, Hans (*Inst. de Méd. et de Chirurgie expérimentales, Univ. de Montréal, Montreal, Canada*): ANTICORTISOL ACTION OF ALDOSTERONE. Science *121*:368-69, March 11, 1955.

The author, who has postulated the medical importance of a proper balance between gluco- and mineralocorticoids, presents direct experimental observations that two opposing, naturally secreted corticoids can regulate the course of biologic phenomena, including inflammation. Hydrocortisone and aldosterone were administered to adrenalectomized rats in which "granuloma pouches" were prepared and inflammation induced by injections of croton oil and evaluated after 14 days. It was noted that the natural mineralocorticoid aldosterone inhibited the actions of the natural glucocorticoid cortisol in the proportion 1:8, with respect to volume of inflammatory exudate, gain in body weight, and involution of spleen and thymus.

Smith, M. J. H.; and Taylor, K. W. (*Dept. of Chem. Path., King's Coll. Hosp. Med. Sch., London, England*): BLOOD CONCENTRATIONS OF PYRUVIC AND ALPHA-KETOGLUTARIC ACIDS IN NORMAL PEOPLE AND DIABETIC PATIENTS. Lancet *1*:27, Jan. 1, 1955.

In this series of patients, the diabetes was not associated with any disturbance of the blood levels of pyruvic or *a*-ketoglutaric acids over a wide range of blood glucose concentrations.

Suomalainen, Paavo (*Zoological Lab., Univ. of Helsinki, Helsinki, Finland*): MAGNESIUM DIABETES. Acta physiol. scandinav. *31*:51-52, 1954.

Histological studies show that in the hedgehog, the

rat, and the mouse, injections of magnesium cause changes in the ratios of the alpha and beta cells in the islets of Langerhans. Like alloxan, magnesium damages the beta cells, so that the ratio of alpha cells to beta cells is changed in favor of the alpha cells. In the guinea pig, however, no change could be established.

Van Bruggen, J. T.; Yamada, P.; Hutchens, T. T.; and West, Edward S. (*Dept. of Biochem., Univ. of Oregon Med. Sch., Portland, Ore.*): LIPOGENESIS OF THE INTACT ALLOXAN-DIABETIC RAT. J. Biol. Chem. *209*:635-40, August 1954.

Acetate-1-C^{14} label incorporation was studied in control and diabetic intact rats. The defect in fatty acid lipogenesis of the diabetic rat was confirmed. Incorporation of label into cholesterol fractions of liver, gut, carcass, and skin approximated control figures. Tissue cholesterol concentrations of diabetics were essentially identical to control figures. The data suggested to the authors that cholesterologenesis remained unaltered in the alloxan-diabetic preparations studied. The incorporation of label into fatty acids of the fasted or nonfasted diabetic rat was of the same order of magnitude as the incorporations of fasted control rats.

Vartiainen, Ilmari; and Paasonen, Matti (*Second Med. Clin., Univ. of Helsinki, Helsinki, Finland*): INFLUENCE OF TYROSINE ON FOOD SELECTION IN ALLOXAN DIABETES. Ann. med. int. Fenniae *43*:341-45, 1954.

A group of 9 alloxan-diabetic rats and 10 normal rats was kept on a self-selection diet for 8 to 14 weeks. Tyrosine administered subcutaneously (1 gm. per kg. of body weight once daily for two weeks) and perorally (5 gm. per kg. of body weight once daily for two weeks) lowered the sucrose intake, especially of the diabetic animals. The subcutaneous administration also produced an increase in the blood sugar.

Vartiainen, Ilmari; and Paasonen, Matti (*Second Med. Clin., Univ. of Helsinki, Helsinki, Finland*): SELECTION OF CASEIN, GELATIN AND KERATIN IN ALLOXAN DIABETES. Ann. med. int. Fenniae *43*:324-28, 1954.

Fourteen healthy rats were kept on a self-selection diet, in which the calorie sources were casein, gelatine, keratin, olive oil, and sucrose. After a period of 14 days to accustom the rats to the diet, their dietary selection was observed for a control period of 28 days. They were then rendered diabetic with alloxan. When a definite craving for protein had developed, a test period of 28 days was started. During the period with diabetes, the rats ingested the same amounts of sucrose and olive oil as when healthy. The casein intake increased fivefold. The gelatin and keratin intakes were low during both the normal control period and the period with diabetes. The craving for protein in the diabetic rats appears to be specific and is not directed toward any protein generally.

Vere, D. W.; and Verel, D. (*Med. Unit, London Hosp., London, England*): RELATION BETWEEN BLOOD SUGAR LEVEL AND THE OPTICAL PROPERTIES OF THE LENS OF THE HUMAN EYE. Clin. Sc. *14*:183-96, May 1955.

Increasing blood sugar is shown to be associated with dimming of the red reflex of the eye in normal and diabetic human subjects. The changes are due to a reversible opacification of the front of the lens of the eye. It is suggested that these changes in the lens may be partly responsible for the transient dimness of vision noted by diabetic subjects while hyperglycemic and may be related to the formation of true diabetic cataract.

Weidmann, Hans (*Res. Labs., H. Lundbeck and Co., A/S, Copenhagen, Denmark*): THE EFFECT OF POLYPHLORETIN PHOSPHATE ON THE ABSORPTION OF INSULIN. Acta endocrinol. *18*:81-86, January 1955.

Polyphloretin phosphate, a highly active hyaluronidase inhibitor, markedly delays the blood sugar depressing activity of insulin in rabbits.

Wrenshall, Gerald A.; Andrus, Stephen B.; and Mayer, Jean (*Banting and Best Dept. of Med. Res., Univ. of Toronto, Toronto, Canada, and Dept. of Nutrition, Harvard Sch. of Pub. Health, and Dept. of Path., Harvard Med. Sch., Boston, Mass.*): HIGH LEVELS OF PANCREATIC INSULIN COEXISTENT WITH HYPERPLASIA AND DEGRANULATION OF BETA CELLS IN MICE WITH THE HEREDITARY OBESE-HYPERGLYCEMIC SYNDROME. Endocrinology *56*:335-40, March 1955.

The obese-hyperglycemic syndrome of mice is characterized by an increase in the extractable insulin of the pancreas as well as hyperplasia and degranulation of the beta cells. These findings appear consistent with a primary hypersecretion of glucagon and secondary hypersecretion of insulin in this syndrome postulated and supported by two of the authors (J. M. and S. B. A.). However, the direct measurements of the rates of secretion of insulin and glucagon necessary to confirm this hypothesis have not been made. The fact that beta cells with stainable granules and extractable insulin are found in the pancreases of some maturity-onset diabetic human subjects in amounts which approach and occasionally exceed the average values for these factors in nondiabetic man provides a limited parallel with the above findings in the obese-hyperglycemic mouse.

EDITORIALS

FUND RAISING

Elsewhere in this issue appear two Committee reports that contain seemingly conflicting recommendations. The report of the Committee on Policies recommends that the Council reaffirm its opposition to general public fund raising by the national organization and its affiliates. Unanimous acceptance of this report by the Council on June 3, 1955, established this recommendation as the official, continuing policy of the American Diabetes Association.

The report of the Committee on Finance, on the other hand, recommends by majority vote favorable consideration of general public fund raising. This recommendation, when presented to the Council on June 3, 1955, was neither rejected nor accepted but referred instead to the Executive Committee for further study.

Failure of the Council to reject outright the recommendation of the Committee on Finance, which it logically might have done in view of its previous action, reveals that, while the majority are still opposed to general public fund raising, opinion is by no means unanimous.

The basic issue is whether a program of limited fund raising among "diabetics, their families and friends," approved by the Council in 1954, can provide the Association with even the modest financial resources that its activities require. The Council, for the present, is committed to this approach, and means of implementing it are being developed as rapidly as possible. If it fails, the movement toward general public fund raising, with its far-reaching implications for the future of this Association, will doubtless be accelerated. The subject will continue to receive the closest attention of the Council and its Committees with the help and advice of the Affiliates.

HENRY T. RICKETTS, M.D., *President*
American Diabetes Association

READER INTEREST SURVEY

DIABETES, *The Journal of the American Diabetes Association,* has now completed four years of publication. As with all new publications, it has had its share of trials and tribulations, but nevertheless steady progress and improvement have been made, and it is the consensus of the publications committee and the editorial board that the *Journal* is a success. It has established itself as a publication which admirably meets the special needs of the members of the Association in whose interest it was conceived.

In order to make a broadly-based estimate of the progress of DIABETES and to re-evaluate its objectives and accomplishments, the Reader Interest Survey Questionnaire was mailed to all subscribers, both members and nonmembers of the American Diabetes Association. An unusually large and gratifying number of replies—almost 900—were received and have been carefully analyzed by a professional statistician. In addition, there have been innumerable suggestions for improvement of the *Journal,* including requests for special articles and departments. The many constructive criticisms received from members have been of great value to the committee and editors in planning the future course and development of the *Journal.*

Over 82 per cent of all readers who answered the questionnaire considered the *Journal* "good" to "excellent" in quality, with only 16 per cent rating it "average" or "poor." More readers think it is "good" than "excellent," however, 46 per cent scoring it "good" and 36 per cent "excellent." Over half the readers considered the balance about right between articles dealing with practical clinical matters and those concerned with experimental laboratory procedures and investigations. Over one-fourth of the readers complained that there were too many reports on experimental laboratory work, 28 per cent voting in this category. Only 3 per cent stated that the contents favored too many clinical problems. Four-fifths (81 per cent) considered the style satisfactory.

The department "Diabetes Abstracts" received the general vote of "good" from 40 per cent of the voters and 37 per cent regard it as "excellent"; 41 per cent voted editorials generally "good," and 37 per cent rated them "excellent." Biographical historical notes received a vote of "good" from 36 per cent and "excellent" from 27 per cent. Statistics were rated "good" by 36 per cent, with 21 per cent of the voters considering them "excellent." The organization section was rated "good" by 36 per cent, and "excellent" by 19 per

cent. News of Affiliate Associations was rated "good" by 32 per cent of readers, "excellent" by 16 per cent, and "fair" by 10 per cent. News Notes and Personals scored "good" by 32 per cent, "excellent" by 18 per cent, and "fair" by 10 per cent.

Of the five types of articles published in DIABETES, clinical reviews were favored by 56 per cent of the readers. Close behind came original clinical studies with a vote of 52 per cent, and next were physiological and biochemical reviews with 47 per cent of readers asking for more. Case reports and original scientific papers rate about even, 31 per cent and 30 per cent respectively.

An overwhelming percentage of members answering the questionnaire (69 per cent), specialize in internal medicine and the next largest group (9 per cent) is composed of general practitioners. The remaining 22 per cent is divided into research workers, teachers, and various specialists.

The replies were also broken down according to geographical areas as well as separated into members and nonmembers. Generally, the areas of most dense population, in the East, the West, and the Midwest, were less enthusiastic in their reception of the *Journal* than the outlying areas of less dense population. Over half of the foreign readers were enthusiastic, with a few less voting for "good" and only 5 per cent in the "average" column, and none unfavorable. This indicates that physicians near the large medical centers rate the *Journal* lower than do physicians in small urban and rural areas. There were no great differences between the reactions of the members of the American Diabetes Association and nonmembers, except that the nonmembers tended to rate the publication more highly than did the members.

A repeated complaint by readers concerned the lateness of the *Journal*. This was already under study at the time of the survey and the present schedule is picking up production time with each issue so that publication dates should be on time early in 1956. Another undercurrent of criticism was that outside sources of published material are not sufficiently utilized. (The editors welcome and actually solicit contributions from all sources.)

Continued improvements in format and contents, based on the survey, have been discussed and planned by the editorial board. Many of these will undoubtedly appear in the next volume. Obviously, on the basis of such favorable survey statistics, no drastic change of approach is indicated. Nevertheless, the very thoughtful, critical comments and specific suggestions of members have now become available for editorial consideration and guidance, and will be utilized in developing future policies of improvement.

FRANKLIN B. PECK, SR., M.D., *Secretary*
American Diabetes Association

ARTIFICIAL SWEETENERS

The general public in the United States has become aware of the obesity problem. The lay press, radio and television are expounding the virtues of many food and beverage preparations with decreased caloric content. The bulk of these caloric cuts are based upon the use of nonnutritive sweeteners to replace sugar. The acceptance of canned fruits flavored with artificial sweeteners is manifested by the figures of the food processors; these fruits have been popular in contrast to the old water-packed fruits. The use of artificial sweeteners in the carbonated beverage industry has been even greater than in the canning industry.

The Food and Drug Administration has taken recognition of this extended use of the artificial sweeteners. This organization requested the Food and Nutrition Board of the National Research Council to render an opinion on the nutritional and public health problems involved in the growing distribution of foods containing nonnutritive artificial sweeteners in the place of sugar and other nutritious sweeteners. Specific consideration was given to saccharin and cyclohexylsulfamates.

The Food and Nutrition Board's report opens with the statement, "Recognition is given to the usefulness of safe artificially sweetened foods for the special dietary purposes of individuals who must restrict their intake of sugar, e.g., diabetics." The Board further recommends that "nonnutritive sweeteners be used only for special dietetic purposes and that necessary precautions governing their preparation and distribution be formulated."

The physiological harmlessness of saccharin at levels of maximum probable intake the Board considers has been established. This judgment is based upon its use for over fifty years. The more recently introduced artificial sweetener, "Cyclamate" (Sucaryl), does not have the test of time behind it, nor is its tolerance level known. The Committee of the Board, in its first report, stated that it was impressed with the fact that the "Cyclamate" has physiological activity in addition to its sweetening effect. The Committee concludes that ". . . . it is reasonably certain that no nutritional or public health problem will result from the approval of the carefully regulated use of the 'Cyclamate' as a nonnutritive sweetener in 'special purpose' foods." Newer preparations which incorporate the "Cyclamate" with the saccharin give an even greater margin of safety.

HERBERT POLLACK, M.D., *Chairman*
Committee on Food and Nutrition
American Diabetes Association

Accepted by the Council at the Fifteenth Annual Meeting in Atlantic City June 3-4, 1955.

Correspondence

POLICIES OF THE AMERICAN DIABETES ASSOCIATION

To the Editor:

The temptation to engage in solicitation of money from the public by the use of mass publicity channels has faced the governing body of this Association ever since it embraced the twin projects of education of the public about diabetes and detection of unrecognized cases. Successive administrations have affirmed and recently reaffirmed a policy which avoids open and unrestricted fund raising. The obvious needs for money are for research, to expand and improve our program of dissemination of authoritative information about diabetes to diabetics and to the general public, to support our two journals (lay and professional), and to employ additional staff to carry out these and other worthy projects. If the pattern of other, better known health agencies was followed there is little doubt that major increases in income would result and the organization would become better known by the general public.

In spite of such potential financial rewards the Council of the Association, advised by its Policies committees from year to year, has chosen to follow a course counter to the common one. The wisdom of this policy, or lack of it, as the case may be, will not be apparent until some years have elapsed, the work of the Association carefully analyzed, and our prestige properly appraised in comparison with the record of other special groups with more money to raise and to spend.

Proponents of a somewhat unpopular policy such as this have convinced the Council of the wisdom of several fundamental principles which are pertinent to the problem.

First, there is the obvious fact that we, as an organization, can elect to use public fund-raising methods at any time we choose. But having elected to do so we cannot retreat to more conservative policies. Once adopted, those methods must continue by virtue of the existence of the organization they support. Only a catastrophe of some kind could change them.

Second, it is apparent that radical change should come slowly—by evolution, not revolution. As growth occurs it is more solid if it is slow and steady. Mushrooming growth tends to be soft and porous.

Again, any medical organization in which control of principle and purpose is not held rigidly by the physicians who compose it, may not accomplish what it sets out to do. It is axiomatic that if devoted people fail to participate actively in the work of an organization their skill, talent, wisdom, and sympathies and interest are lost.

Money should not be raised for the purpose only of obtaining it, especially by a nonprofit association. Specific uses should be recognized, budgets established and funds sought to fulfill those needs. Otherwise harm may result because of extravagance and covetousness. Money can bring evil as well as good, and there are many things which it cannot buy. Included in these are good will, confidence, self-respect, and most important, the faithful services of many people devoted to a common cause.

Perhaps the most cogent argument in favor of more income is the need for support of research. Yet governmental and other agencies now make money available in unprecedented amounts. Many observers believe that the current need is not for more financial support but for more capable investigators—for brains more than for facilities.

Finally, it must not be forgotten that it is possible to grow better instead of bigger. There are times when emphasis might well be on improvement of quality rather than expansion of quantity. The active program now promoted by this Association includes projects like the journals, postgraduate courses, affiliate societies, diabetic camps, and case-finding endeavors, perfection of which could well engage our major attention for the next few years. In most instances they require consecrated effort by physicians, not more money. They need the kind of help which money cannot buy.

We have a fifteen year record of achievement of which we may well be proud. It has occurred without use of the familiar appeal to the public for money. Perhaps it is now time to consolidate our gains, to improve rather than increase. A radical change of policy might easily create new problems and undo some of the good work which has resulted from fifteen years of hard work in our present pattern.

This comment primarily represents the viewpoint of its writer, but it is shared by many others who have the good of the organization at heart. Certainly its merit should be weighed carefully before any change of method is considered seriously.

ARTHUR R. COLWELL, M.D.
Chairman, Department of Medicine
Northwestern University Medical School
Chicago, Illinois

June 15, 1955

HYPOPHYSECTOMY AS PREVENTIVE THERAPY OF DIABETIC COMPLICATIONS

To the Editor:

In my paper "Prevention of Vascular Disease in the Diabetic" in DIABETES, July-August, 1955, on page 301, appears the statement: "In our limited experience, unequivocal improvement in retinopathy and probably improvement in nephropathy appear to follow hypophysectomy in diabetic patients with advanced vascular disease."

In another paper presented at the meeting of the American Diabetes Association in June, 1955,* my associates and I stated: "Much more time must elapse before it will be possible to determine whether, under suitable conditions, hypophysectomy will retard the progress of diabetic vascular disease."

The paper in the July-August issue of DIABETES was written in the autumn of 1954. Unfortunately, the galley proofs arrived and were returned during my absence in the summer of 1955. But for this, the first statement noted above would have been changed for the following reasons:

1. *Some* diabetics following hypophysectomy appear to have "unequivocal improvement" in the retinal vascular lesions; but others have progression of their retinal pathology. It is our *belief* that the improvement or lack of improvement is dependent upon the state of the retinal vessels at the time hypophysectomy is performed, that is, improvement follows in those patients whose vascular lesions are not too far advanced. However, we do not *know* that this is true, nor will we for several years.

2. During the past year, we have become increasingly concerned over the rising tide of enthusiasm for hypophysectomy in diabetics in general. It was for this reason that we went out of our way in the paper which was presented at the June meeting to indicate that no one as yet is able to make any positive statements regarding the value of the procedure; and also emphasized the hazards involved and our opinion that the procedure was probably not indicated either in those with advanced renal disease, or in the patient without a significantly unstable, insulin-resistant diabetes.

LAURANCE W. KINSELL, M.D.
Institute for Metabolic Research
Highland Alameda County Hospital
Oakland, California

*To be published in an early issue of DIABETES.

A Definition of Diabetes Mellitus

Those who adhere to the unitarian conception of diabetes, as I do, define this disease as an abnormality of metabolism created by insufficiency of the insular activity of the pancreas. In diabetes the homeostasis of the blood sugar level is permanently disturbed. In cases of severe diabetes in which no treatment is employed, abnormal elevation of the blood sugar level is a constant phenomenon. In cases in which the disease is of mildest intensity, abnormal elevation regularly is provoked by administering dextrose. In this characteristic, which, as I interpret it, represents evidence of irreparable disease, clinical diabetes differs most consistently from all other conditions associated with hyperglycemia. Disorders of other glands of internal secretion or of the liver or of the central nervous system, individually or collectively, are capable of disturbing the level of the blood sugar, but the hyperglycemia or tendency to elevation of the blood sugar level in such conditions is impermanent, whereas that in diabetes is permanent except as it may be controlled by restricting the intake of food or by giving insulin.

By Russell M. Wilder, M.D., in *Clinical Diabetes Mellitus and Hyperinsulinism,* Philadelphia, W. B. Saunders Co., 1940, p. 19.

J. J. R. Macleod

Frank N. Allan, M.D., Boston

Twenty years ago, on March 16, 1935, the death of John James Rickard Macleod brought to a close the career of one of the most distinguished physiologists of his time. He was noted for original research in the physiology of respiration and metabolism, for his success as a teacher of undergraduate and graduate students, for the clarity of his scientific writing and for his leadership in teaching the clinical application of physiology and biochemistry. To physicians with a special interest in diabetes he became well known for his own researches in carbohydrate metabolism and particularly for the opportunity which he gave to Banting and Best to carry on in his laboratory the work which led to the discovery of insulin.

Macleod was born in Scotland on Sept. 6, 1876, the son of a minister of Aberdeen. He graduated from the medical school of Aberdeen University with honors in 1889. He received the Anderson Travelling Fellowship which gave him an opportunity to study in Leipzig and Berlin. Later he studied at Cambridge, receiving the D.P.H. He became a demonstrator in physiology and later lecturer in biochemistry at the London Hospital Medical School. In 1901, he was the McKinnon Research Scholar of the Royal Society. In 1903, at the age of twenty-seven, he became Professor of Physiology at Western Reserve University in Cleveland. In 1918, he became Professor of Physiology at the University of Toronto and Assistant Dean of the Faculty of Medicine. He left Toronto in 1928 to become the Regius Professor of Physiology at his alma mater in Scotland.

Macleod's first physiological researches were concerned with the intracranial circulation, a subject which he investigated in cooperation with Leonard Hill, the outstanding English physiologist at the turn of the century. His attention was next directed to the control of respiration, a study which he continued from 1902 to 1922. In 1908, he became interested in experimental glycosuria and in 1913 he published a book on diabetes and its pathological physiology. In 1921 his studies were concerned with the control of the blood sugar level in normal and depancreatized animals and the role played by the liver and also the pancreas in the metabolism of sugar.

Physiology and Biochemistry in Modern Medicine was the title of the textbook first published in 1918, which extended widely Macleod's reputation as a medical teacher. This textbook, which was welcomed by students in Toronto and in medical schools in other parts of the world as well as by practicing physicians, went through seven editions in less than two decades.

In speaking of Macleod's appointment to the Chair of Physiology at the University of Toronto, Sir Henry Dale[1] said: "Macleod's tenure was of course to be one of historic importance for the world reputation of the Department and of the Medical School to which it belonged and, less directly, for the advancement everywhere of physiology and experimental medicine. He succeeded to a Department unusually well equipped by the standards of those days for research in the general field of physiology including that of his own special interest

in the problems of carbohydrate metabolism.'

'In this special field Macleod had himself already made some sound experimental contributions to the then generally accepted canon of knowledge; and there could have been few, if any, who had a better command than his of the numerous literature of the researches and theories which dealt with it. When young Frederick Banting, therefore, with a recent surgical experience from war service and little more than a student's knowledge of physiology, came asking, with a burning eagerness and a sense of a mission for an opportunity to make a new attempt to obtain from the islets of the pancreas, the hormone insulin, the production of which speculation had long credited them, Macleod was well qualified to give him a discouraging account of the failure of many earlier attempts, most of them by workers of a much riper experience. It was a fair and proper warning; and it is to be counted to Macleod's lasting credit that having given it, he agreed nevertheless, to give Banting also the desired opportunity. Possibly he had seen that methods then newly available for measuring the minute quantities of glucose present in small samples of blood, might have produced a significant improvement in the chances of success for a further attack on such a problem. And it should be further remembered in any case that Macleod had produced a class of students well trained in these new methods of microanalysis and in determinations of the respiratory balance of oxygen consumed and carbonic acid exhaled.'

'It was Macleod also, who saw that if Banting's attempt was to give any intelligible result, he must have the cooperation of somebody with this recent biochemical training; and this recommendation was responsible for bringing Charles Best, recently graduated in Science, trained in the necessary biochemical methods, and himself rendered eager by a family contact with diabetes, to do something for those whom it afflicted, into the historic collaboration. Frederick Banting supplied on his part the determined unquenchable initiative and an equipment with the necessary surgical technic. The collaboration was to be one of intimate understanding, with no question between the two participants of any but an equal sharing of its success . . ."

Professor Velyien E. Henderson,[2] one of Macleod's colleagues in the Faculty of Medicine at Toronto, also wrote of Macleod's prestige in research on carbohydrate metabolism when he joined the University of Toronto: "Soon his laboratory attracted a group of young workers in physiology. It was due to Professor Macleod's established reputation as an authority on carbohydrate metabolism that Dr. Banting, now Sir Frederick, came to Toronto to consult him and to pursue his investigations on the pancreas with the assistance of C. H. Best, then a young assistant who eventually succeeded Professor Macleod as Professor of Physiology at the University of Toronto. These investigations led to the brilliant and important discovery of insulin by Dr. Banting and Dr. Best.'

'With the aid of Dr. J. B. Collip, the first stages of purification of insulin were undertaken and arrangements made for its commercial production. . . .'

'In recognition of this very important discovery, Dr. Banting and Professor Macleod were awarded jointly the Nobel Prize, the former sharing the award with Dr. Best and the latter with Dr. Collip."

The discovery of insulin was followed by intensive research in the Department of Physiology as efforts were made to investigate the physiologic functions of insulin, and to use it as a tool to uncover and disentangle some of the secrets of metabolism. As a senior medical student at the University of Toronto, I had witnessed the first use of insulin in the treatment of human diabetes. I had seen the emaciated almost moribund 14-year-old boy selected for the initial trial respond as by a miracle to the treatment started on Jan. 11, 1922, and I was aware of the exciting activities under way in Macleod's laboratories. I therefore accepted eagerly a Fellowship in Physiology which was offered me on graduation and which led to an opportunity to serve for a period of three years as a member of Macleod's team. Thus I became well acquainted with the man who wore the Professor's gown. My personal memories of Macleod recall a man who sought to give his assistants a free opportunity to develop their own ideas and to work out their experiments independently, who offered guidance, without dominance, and who was generous in providing opportunities for participation in scientific meetings (and on one occasion at least in providing personal financial assistance for travel to a distant meeting).

Macleod received many honors. He became President of the American Physiological Society in 1922 and of the Royal Canadian Institute in 1925. He was a Fellow of the Royal Society of Canada, a Fellow of the Royal Society in England, and a Fellow of the Royal College of Physicians. He received the honorary degree of Doctor of Science from the University of Toronto and of Doctor of Laws from the University of Aberdeen. His greatest honor was the esteem of his students, assistants and colleagues.

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[1] Dale, H. H.: Address at Special Convocation, University of Toronto. Diabetes 3:30-35, January-February 1954.

[2] Henderson, V. E.: Obituary. J. J. R. Macleod. Science *81*: 355, April 12, 1935.

ORGANIZATION SECTION

Fourth Postgraduate Course in Diabetes and Basic Metabolic Problems

Dallas, Texas, Jan. 25-27, 1956

The American Diabetes Association will offer its Fourth Postgraduate Course in Diabetes and Basic Metabolic Problems in Dallas, Texas, Jan. 25, 26 and 27, 1956, at the new Statler Hilton hotel. The Course will be held under the directorship of Edwin L. Rippy, M.D., Associate Professor of Clinical Medicine, Southwestern Medical School of the University of Texas and Baylor University Hospital, Dallas, Texas. Members of the Local Committee on Arrangements are Lawrence Cameron, M.D., David W. Carter, Jr., M.D., John S. Chapman, M.D., Leonard J. Flohr, M.D., Jabez Galt, M.D., Arthur Grollman, M.D., E. Russell Hayes, M.D., George M. Jones, M.D., Robert K. Portman, M.D., and Donald W. Seldin, M.D.

Developed by the Association's Committee on Professional Education under the Chairmanship of Garfield G. Duncan, M.D., the Course is open to members of the medical profession. It is offered in cooperation with the Southwestern Medical School of the University of Texas, the Dallas Academy of Internal Medicine, and the Dallas Diabetes Association.

FEES: $40 for the three-day Course for members of the American Diabetes Association; $75 for nonmembers. The full fee is payable at the time of filing application for the Course and will be returnable by the Association to any registrant who submits his withdrawal in writing not later than January 10.

Graduate students, fellows, residents, interns and medical students engaged in full-time study in medicine and allied sciences in the local schools and hospitals may attend without charge upon presentation of a letter requesting their admission from their dean or the head of their department or service.

REGISTRATION: An application form is attached to the preliminary program and should be filled out and mailed, together with the fee, as soon as possible. Registrations will be accepted in the order received and will be officially confirmed.

HOTEL ACCOMMODATIONS: The Statler Hilton will serve as the headquarters hotel. Reservation cards will be sent to registrants with their matriculation card confirming acceptance for the Course.

THE FOLLOWING TOPICS AND DISCUSSIONS (SUBJECT TO CHANGE) WILL BE COVERED DURING THE 3-DAY COURSE.

WEDNESDAY, JANUARY 25

ORIENTATION — PATHOLOGICAL PHYSIOLOGY: Chairman, Henry T. Ricketts

8:00 Registration
9:30 Physiological Observations in Diabetes—Arthur Grollman
10:00 Biochemical Considerations—Morton F. Mason
10:30 Intermission
10:40 Endocrine Influences in Carbohydrate Metabolism—Jerome W. Conn
11:10 Islet Pathology in Diabetes—W. Stanley Hartroft
11:40 to 12:00 Discussion by Registrants
12:15 to 2:15 Round Table Luncheon (by subscription)—Questions and Answers: Chairman, Edwin L. Rippy
Guests: Charles H. Best, Arthur Grollman, Morton F. Mason, Jerome W. Conn, W. Stanley Hartroft

CLINICAL DIABETES: Chairman, Henry B. Mulholland

2:30 Diagnostic Criteria—Joseph T. Beardwood, Jr.
2:50 Insulin—Charles H. Best
3:20 Physician-Patient Relationship in the Successful Management of Diabetes—Alexander Marble
3:40 Intermission
3:50 The Dietary Regime—Herbert Pollack
4:20 Emotional Factors—Stewart Wolf
4:50 to 5:00 Discussion by Registrants
6:30 Social Hour (by subscription)
7:30 Banquet—Edward L. Bortz, Presiding
Entertainment—Talent Show

THURSDAY, JANUARY 26

CLINICAL DIABETES: Chairman, William H. Olmsted

9:00 Teaching the Diabetic Diet—Mrs. Rosa Macri Adair, Miss Harriet Pruitt and Associates. Demonstration

9:30 Diabetes in Childhood—Robert L. Jackson

10:00 Diabetes in Childhood—Discussion—George M. Guest

10:20 Prognosis in Childhood Diabetes—Priscilla White

10:40 Intermission

10:50 Chemistry and Action of Available Insulins—Franklin B. Peck, Sr.

11:05 Therapeutic Applications of Available Insulins—Arthur R. Colwell

11:30 Prevention and Management of Keto-Acidosis Donald W. Seldin

12:15 to 2:15 Round Table Luncheon (by subscription): Chairman, George M. Jones

Panel Discussion—"Diabetes and Pregnancy" Participants: Priscilla White, Blair Holcomb, George M. Guest, Robert L. Jackson, Jules Vieaux

CLINICAL DIABETES: Chairman, Frederick W. Williams

2:30 Initiation of Diabetic Control in Adults—Garfield G. Duncan

3:00 Diabetes in the Aged—Henry B. Mulholland

3:20 Insulin Allergy and Its Clinical Management—John H. Warvel

3:40 Intermission

4:00 to 5:00 Registrant Participation—Lectures, Demonstrations and Clinics (Chairmen will be moderators for discussion) (Registrants will ask for these panel discussions at the time of registration)

Room A—Experimental Background of Present Knowledge of Diabetes. Chairman: Lawrence Cameron; Francis D. W. Lukens, Arthur Grollman.

Room B—Urine and Blood Tests in Diabetes. Chairman: Robert K. Portman; George M. Guest, Morton F. Mason.

Room C—Treatment of Diabetic Ketosis. Chairman: E. Russell Hayes; Donald W. Seldin, Jerome W. Conn.

Room D—Calculating the Diabetic Diet. Chairman: Leonard J. Flohr; Mrs. Rosa Macri Adair, Miss Harriet Pruitt and Associates, Randall G. Sprague.

Room E—Renal Disorders and Diabetes. Chairman: W. Grady Reddick; Frank N. Allan, Paul J. Thomas.

6:30 Social Hour—Sponsored by the Dallas Diabetes Association and Dallas Academy of Internal Medicine

FRIDAY, JANUARY 27

CLINICAL DIABETES: Chairman, John A. Reed

9:00 Management of the Diabetic in Periods of Stress, Surgery or Infection—Henry M. Winans

9:30 The Past, Present and Probable Future of Diabetes—Charles H. Best

10:00 A Follow-Up Study of Below Knee Amputations in Diabetics—Beverly Chew Smith

10:30 Intermission

10:40 Skin Disorders in Diabetes—Everett C. Fox

11:00 The Brittle Diabetic—E. Paul Sheridan

11:20 General Summary—Garfield G. Duncan

11:40 to 12:00 Discussion by Registrants

12:15 to 2:15 Round Table Luncheon (by subscription)—Questions and Answers: Chairman, David W. Carter, Jr.

Guests: Henry M. Winans, Charles H. Best, Beverly Chew Smith, Everett C. Fox, E. Paul Sheridan, Garfield G. Duncan

COMPLICATIONS OF DIABETES: Chairman, Randall G. Sprague

2:30 Diabetic Neuropathies—James A. Greene

3:00 Theories of the Pathogenesis of Degenerative Vascular Complications—Henry T. Ricketts

3:30 Intermission

3:45 Multiple Informal Seminars:

Degenerative Vascular Complications in Diabetes

(Chairmen will participate as moderators.) (No choice—Groups designated by General Chairman.)

Chairman: J. Shirley Sweeney. Panel: Henry T. Ricketts, J. Harold Cheek (Surgery), Oscar Marchman, Jr. (Eyes).

Chairman: George M. Jones. Panel: George J. Hamwi, Dale J. Austin (Surgery), Maxwell Thomas (Eyes).

Chairman: David W. Carter, Jr. Panel: James T. Wortham, Jesse E. Thompson (Surgery), Lester H. Quinn (Eyes).

Chairman: Jabez Galt. Panel: Raymond L. Gregory, Hudson Dunlap (Surgery), Harold M. Block (Eyes).

Chairman: Robert K. Portman. Panel: Frederick W. Williams, Leroy J. Kleinsasser (Surgery), Carroll W. Browning (Eyes).

4:45 Assembly—Final Discussion

8:00 Meeting of Lay Society—Dallas Diabetes Association. Chairman: Mr. R. B. Moreland, Jr., President

Panel: Charles H. Best, Randall G. Sprague, Henry T. Ricketts, Alexander Marble, Thomas P. Sharkey

FACULTY OF THE FOURTH POSTGRADUATE COURSE

FRANK N. ALLAN, M.D., *Executive Director, Medical Department, Lahey Clinic; Member, Medical Administrative Board, New England Deaconess Hospital, Boston, Massachusetts.*

DALE J. AUSTIN, M.D., *Clinical Assistant Professor of Surgery, Southwestern Medical School of the University of Texas; Baylor University Hospital, Dallas, Texas.*

JOSEPH T. BEARDWOOD, JR., M.D., *Professor of Metabolic Diseases, Graduate School of Medicine of the University of Pennsylvania; and Director, Metabolic Division, Graduate Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania.*

CHARLES H. BEST, C.B.E., M.D., F.R.S., *Professor of Physiology; Director and Professor in the Banting and Best Department of Medical Research, University of Toronto, Toronto, Ontario, Canada.*

HAROLD M. BLOCK, M.D., *Clinical Assistant Professor, Ophthalmology, Southwestern Medical School of the University of Texas; Baylor University Hospital, Dallas, Texas.*

EDWARD L. BORTZ, M.D., *Associate Professor of the Graduate School of the University of Pennsylvania; Chief, Medical Service "B," The Lankenau Hospital, Philadelphia, Pennsylvania.*

CARROLL W. BROWNING, M.D., *Professor and Chairman, Division of Ophthalmology, Southwestern Medical School of the University of Texas; Chief, Department of Ophthalmology, Parkland Memorial Hospital, Dallas, Texas.*

LAWRENCE C. CAMERON, M.D., *Clinical Assistant Professor of Medicine, Southwestern Medical School of the University of Texas; Parkland Memorial Hospital, Dallas, Texas.*

DAVID W. CARTER, JR., M.D., *Consultant in Internal Medicine, Southwestern Medical School of the University of Texas; Baylor University Hospital, Dallas, Texas.*

J. HAROLD CHEEK, M.D., *Clinical Instructor in General Surgery, Southwestern Medical School of the University of Texas; Parkland Memorial Hospital, Dallas, Texas.*

ARTHUR R. COLWELL, M.D., *Professor of Medicine and Chairman, Department of Medicine, Northwestern University Medical School, Chicago, Illinois.*

JEROME W. CONN, M.D., *Professor of Internal Medicine and Director, Division of Endocrinology and Metabolism, University of Michigan Medical School, Ann Arbor, Michigan.*

GARFIELD G. DUNCAN, M.D., *Clinical Professor of Medicine, Jefferson Medical College, Director of the Medical Divisions, Pennsylvania Hospital and Benjamin Franklin Clinic, Philadelphia, Pennsylvania.*

HUDSON DUNLAP, M.D., *Clinical Associate Professor of Surgery, Southwestern Medical School of the University of Texas; Senior Attending Surgeon, Baylor University Hospital, Dallas, Texas.*

LEONARD J. FLOHR, M.D., *Clinical Instructor, Internal Medicine, Southwestern Medical School of the University of Texas; Director of Cardiac Clinic, St. Paul's Hospital, Dallas, Texas.*

EVERETT C. FOX, M.D., *Attending Dermatologist, Baylor University Hospital; Consulting Dermatologist, Methodist Hospital, Dallas, Texas.*

JABEZ GALT, M.D., *Clinical Instructor, Internal Medicine, Southwestern Medical School of the University of Texas; Baylor University Hospital, Dallas, Texas.*

JAMES A. GREENE, M.D., *Professor of Medicine, Department of Internal Medicine, Baylor University College of Medicine, Houston, Texas.*

RAYMOND L. GREGORY, M.D., *Professor of Internal Medicine, University of Texas School of Medicine; John Sealy Hospital, Galveston, Texas.*

ARTHUR GROLLMAN, M.D., *Professor, Experimental Medicine, Southwestern Medical School of the University of Texas; Consultant in Internal Medicine, Baylor University Hospital, Dallas, Texas.*

GEORGE M. GUEST, M.D., *Professor of Research Pediatrics, University of Cincinnati College of Medicine; Attending Pediatrician, Cincinnati Children's Hospital, Cincinnati, Ohio.*

GEORGE J. HAMWI, M.D., *Associate Professor of Medicine, Head, Division of Endocrinology and Metabolism, Ohio State University; Head, Section of Endocrinology and Metabolism, University Hospital, Columbus, Ohio.*

W. STANLEY HARTROFT, M.D., *Mallinckrodt Professor and Chairman of the Department of Pathology, Washington University School of Medicine; Pathologist in Chief, Barnes Hospital, St. Louis, Missouri.*

E. RUSSELL HAYES, M.D., *Clinical Associate Professor of Medicine, Southwestern Medical School of the University of Texas; Baylor University Hospital, Dallas, Texas.*

BLAIR HOLCOMB, M.D., *Senior Consultant in Diabetes, University of Oregon Medical School, Portland, Oregon.*

ROBERT L. JACKSON, M.D., *Professor and Chairman, Department of Pediatrics, University of Missouri; Pediatrician in Chief, University Hospitals, Columbia, Missouri.*

GEORGE M. JONES, M.D., *Assistant Professor of Clinical Medicine, Southwestern Medical School of the University of Texas; Baylor University Hospital, Dallas, Texas.*

LEROY J. KLEINSASSER, M.D., *Clinical Associate Professor of Surgery, Southwestern Medical School of the University of Texas; Attending Surgeon and Director of Medical Education, Baylor University Hospital, Dallas, Texas.*

FRANCIS D. W. LUKENS, M.D., *Professor of Medicine and Director, George S. Cox Institute for Medical Research, University of Pennsylvania, Philadelphia, Pennsylvania.*

ALEXANDER MARBLE, M.D., *Assistant Clinical Professor of Medicine, Harvard Medical School; Joslin Clinic and New England Deaconess Hospital, Boston, Massachusetts.*

OSCAR MARCHMAN, JR., M.D., *Clinical Assistant Professor of Ophthalmology, Southwestern Medical School of the University of Texas; Baylor University Hospital, Dallas, Texas.*

MORTON F. MASON, Ph.D., *Professor, Clinical Chemistry, Southwestern Medical School of the University of Texas; Parkland Memorial Hospital, Dallas, Texas.*

HENRY B. MULHOLLAND, M.D., *Assistant Dean and Professor of Internal Medicine, University of Virginia Medical School, Charlottesville, Virginia.*

WILLIAM H. OLMSTED, M.D., *Associate Professor of Clinical Medicine (Emeritus), Washington University School of Medicine; Barnes Hospital, St. Louis, Missouri.*

FRANKLIN B. PECK, SR., M.D., *Associate Professor of Medicine, Indiana University School of Medicine; Consultant in Medicine, Indianapolis General Hospital, Indianapolis, Indiana.*

HERBERT POLLACK, M.D., *Associate Professor, Clinical Medicine, New York University Postgraduate School of Medicine; Associate Physician for Metabolic Diseases, The Mount Sinai Hospital, New York, New York.*

ROBERT K. PORTMAN, M.D., *Clinical Assistant, Internal Medicine, Southwestern Medical School of the University of Texas; Chief, Section on Cardiology, Methodist Hospital, Dallas, Texas.*

LESTER H. QUINN, M.D., *Clinical Professor Ophthalmology, Southwestern Medical School of the University of Texas; Baylor University Hospital, Dallas, Texas.*

W. GRADY REDDICK, M.D., *Clinical Professor of Medicine, Southwestern Medical School of the University of Texas; Baylor University Hospital, Dallas, Texas.*

JOHN A. REED, M.D., *Assistant Clinical Professor of Medicine, George Washington University School of Medicine; Attending Physician, George Washington University Hospital, Washington, D. C.*

HENRY T. RICKETTS, M.D., *Professor of Medicine, University of Chicago; Attending Physician, Albert Merritt Billings Hospital, Chicago, Illinois.*

EDWIN L. RIPPY, M.D., *Associate Professor of Clinical Medicine, Southwestern Medical School of the University of Texas; Baylor University Hospital, Dallas, Texas.*

DONALD W. SELDIN, M.D., *Professor and Chairman, Department of Internal Medicine, Southwestern Medical School of the University of Texas; Chief of the Medical Service, Parkland Memorial Hospital, Dallas, Texas.*

THOMAS P. SHARKEY, M.D., *Assistant Clinical Professor of Medicine, College of Medicine of Ohio State University; Consultant in Internal Medicine and Pathology, Miami Valley Hospital, Dayton, Ohio.*

E. PAUL SHERIDAN, M.D., *Assistant Clinical Professor of Medicine, University of Colorado Medical Center; St. Luke's Hospital, Denver, Colorado.*

BEVERLY CHEW SMITH, M.D., *New York, New York.*

RANDALL G. SPRAGUE, M.D., *Professor of Medicine, Mayo Foundation, Graduate School, University of Minnesota; Consulting Physician, Section of Medicine, Mayo Clinic, Rochester, Minnesota.*

J. SHIRLEY SWEENEY, M.D., *Associate Professor of Clinical Medicine, Southwestern Medical School of the University of Texas; Baylor University Hospital, Dallas, Texas.*

MAXWELL THOMAS, M.D., *Associate Clinical Professor of Ophthalmology, Southwestern Medical School of the University of Texas; Senior Consultant, Veterans Administration Hospital, Dallas, Texas.*

PAUL J. THOMAS, M.D., *Clinical Associate Professor of Medicine, Southwestern Medical School of the University of Texas; Chief of Medicine, Baylor University Hospital, Dallas, Texas.*

JESSE E. THOMPSON, M.D., *Clinical Assistant Professor of Surgery, Southwestern Medical School of the University of Texas; Parkland Memorial Hospital, Dallas, Texas.*

JULES W. VIEAUX, M.D., *Associate Clinical Professor of Obstetrics and Gynecology, Southwestern Medical School of the University of Texas; Baylor University Hospital, Dallas, Texas.*

JOHN H. WARVEL, M.D., *Assistant in Medicine, Indiana University School of Medicine and Diabetic Clinic, Methodist Hospital, Indianapolis, Indiana.*

PRISCILLA WHITE, M.D., *Instructor in Pediatrics, Tufts Medical School; Instructor, Harvard Medical School; New England Deaconess Hospital, Boston, Massachusetts.*

FREDERICK W. WILLIAMS, M.D., *Associate Clinical Professor of Medicine, New York Medical College; Morrisania City Hospital, New York, New York.*

HENRY M. WINANS, M.D., *Emeritus Professor of Medicine, Southwestern Medical School of the University of Texas; Baylor University Hospital, Dallas, Texas.*

STEWART WOLF, M.D., *Professor and Head, Department of Medicine and Consultant Professor of Neurology and Psychiatry, University of Oklahoma School of Medicine, Oklahoma City, Oklahoma.*

JAMES T. WORTHAM, M.D., *Assistant Dean and Associate Professor of Medicine, University of Arkansas School of Medicine; Chief, Endocrine Metabolism Service, University Hospital, Little Rock, Arkansas.*

COMMITTEE REPORTS

Council Sessions, June 3-4, 1955

15th Annual Meeting

Fund-raising Policy

Report of the Committee on Policies:

A meeting of the Committee on Policies was held in Atlantic City, New Jersey, on June 1, 1955. It was attended by Edwin L. Rippy, M.D., Chairman; Henry T. Ricketts, M.D., Vice Chairman; Arthur R. Colwell, M.D., Blair Holcomb, M.D., Henry B. Mulholland, M.D., William H. Olmsted, M.D., John A. Reed, M.D., E. Paul Sheridan, M.D., Randall G. Sprague, M.D., J. Richard Connelly, ex officio, and Mrs. Jessie H. Raborg of the Association staff.

Dr. Edwin L. Rippy, Chairman, who presided, stated that the Committee should discuss the following problems:

1. The proposed new categories of membership—Affiliate Members and Corresponding Members, and methods of presenting them to the Board of Governors and the Assembly of Delegates.

2. The financial situation of the American Diabetes Association at present and in the future and the over-all philosophy of fund raising.

3. A policy regarding establishment of fund-raising activities by the local Affiliates.

4. The question of issuance of charters to the local Affiliates.

There followed a discussion regarding financial needs and goals of this organization and their relationship, as a result of which it was generally decided that the financial needs of the American Diabetes Association are not great, that large sums of money if obtainable could conceivably alter the long existing philosophy of active voluntary participation by physicians and laymen on a national and local level.

More tangibly, it was generally agreed upon that it would be desirable to create an earned income of approximately $300,000; that it would be desirable to become eventually financially independent of contributing corporations and that interpreted into terms of additional income at the present time we might strive to increase such by at least $100,000.

After considerable discussion, the following recom-

mendations were made by the Committee on Policies to the Council:

1. A reaffirmation of our present policy of opposition to public fund raising by the national organization and its Affiliates as previously adopted and defined as follows:

> Any appeal for funds directed to the general public, and the use of any or all of the mass communication media to ask for money must be considered as general public fund raising since it is directed to the public at large. Such media would include newspapers, television, radio, movie theater screens, general mailings, posters, car cards and canisters.

2. The reaffirmation of our intention to continue a campaign of limited fund raising by the Affiliate Associations as outlined by the manual now in preparation if and when approved by the Executive Committee.

3. A recommendation to the Council favoring the principles of issuing charters to Affiliate Associations.

EDWIN L. RIPPY, M.D., *Chairman*

Addendum: The report was presented to the Council on June 3, and was accepted. A member of the Council then moved: "Be it resolved that the Affiliate Associations be urged to intensify their campaigns for increased lay and professional membership; let that be one of their primary objectives." The motion was seconded and unanimously carried.

*Report of the Committee on Finance**

The meeting at Atlantic City, New Jersey, on June 2, 1955, was called to order by the Chairman, Dr. William H. Olmsted. First order of business was reviewing the first meeting of this Committee, held in Philadelphia in January. From that meeting there was one piece of old business, namely, the canvassing of the Affiliate Associations as to what time they considered it best for them to conduct a financial campaign. We had 19 replies from 39 Affiliates. There were two periods that were considered by the Affiliate Associations; one the period of October-November, the other the period of May-June. Grouping the replies under these two periods, we found that for the October-November time there were seven in favor; for the May-June period there were also seven. Unfortunately, some of the strongest Affiliates that we have failed to answer this inquiry and, therefore, it is not of too much significance. The fact remains that those who did reply are almost evenly divided between the fall and the spring.

The Chairman then reviewed the recent financial policy adopted by the Council of the ADA. He read the recommendations verbatim and also reported the meeting of the Committee on Policies and its conclusions which had taken place the preceding day. In the light of these recommendations by the Council, and with the knowledge of the local situations, the Chairman asked the members of the Committee to discuss freely their ideas and opinions regarding the financial policies of the ADA.

The discussion that followed was entered into by everyone present. After lengthy discussion, a committee consisting of Dr. Helen E. Martin of Los Angeles, Dr. Joseph I. Goodman of Cleveland, Dr. Edgar A. Haunz of Grand Forks, N. Dak., and Dr. Christopher J. McLoughlin of Atlanta were appointed to draw up recommendations to the Council. They brought back such a recommendation, and with the help of Dr. Howard F. Root made the following recommendation:

> *The Committee on Finance of the American Diabetes Association strongly recommends to the Council that the plan for fund raising now in effect be broadened to indicate a public appeal for funds. The Committee further recommends that the principles of planned fund raising be defined by the Council, so as to be consistent with local requirements, and also be binding upon Affiliates.*†

This recommendation was voted upon and carried twelve for and seven against. Meeting adjourned.

WILLIAM H. OLMSTED, M.D., *Chairman*

*Accepted by the Council.

†Referred by the Council to the Executive Committee.

"Fund Raising," an editorial by Dr. Henry T. Ricketts, President, American Diabetes Association, appears on the editorial pages of the current issue of DIABETES.

Report of the Committee on Professional Education‡

A meeting of the Committee on Professional Education was held in Atlantic City, New Jersey, on June 2, 1955. It was attended by Randall G. Sprague, M.D., Chairman; George E. Anderson, M.D., Arthur R. Colwell, M.D., E. Perry McCullagh, M.D., Thomas H. McGavack, M.D., Robert H. Williams, M.D., Henry B. Mulholland, M.D., ex officio, J. Richard Connelly, ex officio, and Mrs. Jessie H. Raborg of the Association staff. Edwin L. Rippy, M.D., and Franklin B. Peck, Sr., M.D., were present as guests. The following topics were discussed.

Postgraduate Course Series

1. *Admission of graduate students, fellows, residents, interns and medical students to Postgraduate Courses*

The Committee felt that a policy with respect to the admission of local individuals in these categories should be established. It is therefore recommended to the Council that such individuals on full-time study in medicine and allied sciences in the schools and hospitals of the area in which a Course is held be admitted without charge to the scientific sessions upon presentation of a

‡Accepted by the Council.

letter requesting their admission from their Dean or the head of their department or service.

It is further recommended that a statement outlining this requirement for admission be included in the printed program and in a sign at the registration desk. Such students would be asked to use seats behind those in a restricted or reserved area set aside for the regular registrants of the Course.

2. *Survey of Interests and Qualifications of Registrants at Postgraduate Courses*

The Committee feels that an analysis of the professional interests and qualifications of those attending the Postgraduate Courses would be helpful in planning future Courses. The Committee therefore plans to undertake such an analysis of the members of the Third Postgraduate Course and all subsequent Courses. In the case of the Third Course the survey can be carried out as a project in the National Office. In the case of the Fourth and subsequent Courses, the necessary data can be obtained at the registration desk.

The Committee feels that the submission of such data to each member of the faculty of each Postgraduate Course, covering the members of the immediately preceding Course, would aid him in planning his presentation.

3. *Indoctrination of Faculty Members*

In addition to providing each Faculty member with information regarding the expected character of his audience, it was the opinion of the Committee that those responsible for the planning of each Course should make other efforts to indoctrinate each Faculty member in what type of lecture is most effective and best received in the Courses.

4. *Financial Report of Income and Expenses of Third Postgraduate Course*

A financial report provided by Mr. Connelly was presented concerning the Third Postgraduate Course in Philadelphia on Jan. 19-21, 1955. The Committee was pleased to note that there was an excess of income over expenses of $1,639.84.

5. *Questionnaire to Registrants*

It was the opinion of the Committee that the information submitted by registrants on the questionnaires has been very helpful in evaluating the effectiveness of the first three Postgraduate Courses and that this procedure should be continued. In order to make the questionnaire more easily used by the registrants it was felt that not only the title of each paper should be given as in previous questionnaires, but also the name of the individual presenting the paper. It is understood that the information obtained from the questionnaires will not be circulated outside the Committee on Professional Education and the Council of the Association.

6. *Summaries and Abstracts*

There was considerable discussion of the advantages to the registrants of advance circulation of summaries or abstracts of papers to be presented at the Postgraduate Courses. Dr. Rippy and those associated with him in the planning of the Fourth Postgraduate Course were asked to consider the matter and submit plans to the Committee together with an estimate of the cost of preparation and distribution of such summaries and abstracts.

Fourth Postgraduate Course
Dallas, Texas, Jan. 25-27, 1956

The Committee was pleased to learn from Dr. Rippy that plans for this Course are already well advanced. Dr. Rippy will present a summary of the plans to the Council.

Location of Fifth Postgraduate Course and Council Meeting in January 1957

An invitation to hold the Fifth Postgraduate Course and the Interim Council Meeting in January 1957 in Columbus, Ohio, at the Ohio State Health Center has been received from Dr. George J. Hamwi.

The Committee discussed this and other possible locations and recommends to the Council that Dr. Hamwi's invitation be accepted, providing there are no other suggestions which the Council would like to have considered.

Other Proposed Activities

1. *Survey of teaching of diabetes in American medical schools*

The Committee has not yet begun this survey, but suggests that it be undertaken during the coming summer by the new Committee on Professional Education.

2. *Glossary of terms regarding diabetes, criteria for the diagnosis of diabetes, and classification of different types of diabetes*

The Council recommended at its January 1955 meeting that a special committee be appointed for the preparation of such a glossary, diagnostic criteria and classifications.

It is recommended that the Chairman of the new Committee on Professional Education appoint an appropriate Subcommittee for this activity as soon as feasible.

RANDALL G. SPRAGUE, M.D., *Chairman*

Report of the Committee on Statistics

The work of the Committee during the past year has

been virtually limited to the preparation of the section "Recent Statistics on Diabetes" for the Association's official journal, DIABETES. During the year, such material has been prepared for three issues. In addition to the current information from official sources on mortality for the United States and England and for certain areas within the two countries, the data presented in these issues have included a varied list of topics, such as:

1. Causes of death among insured persons with diabetes.
2. Frequency of diabetes in public school children.
3. Diabetes as a cause of blindness.
4. Mortality from diabetes according to socio-economic level, England and Wales, 1950.
5. Trend of diabetes mortality since adoption of the 6th Revision of the International List of Causes of Death.
6. Comparative mortality by cause among (1) diabetics in the general population, (2) insured persons, and (3) patients of the Joslin Clinic—1954.
7. Recent official statistics on diabetes mortality by sex, age and color.
8. Mortality from diabetes by States.

The Committee has also given statistical advice and information which the Executive Director of the Association has requested from time to time. It has also given occasional service to other Committees of the Association.

In past reports of the Committee, it has made certain recommendations with regard to statistical activities which could profitably be undertaken by the Association. This matter was explored at some length by the Chairman of the Committee with the President and Executive Director of the Association at a conference in April 1955. On the basis of the discussion at this meeting the Chairman plans to prepare specific proposals for presentation to the Council, after consultation with the members of the Committee on Statistics. This matter is still pending.

The Committee welcomes suggestions or material for inclusion in its periodic summary of statistics on diabetes in the official journal of the Association. The Committee is desirous of serving the other Committees of the Association with regard to statistical aspects of their work.

Proposal by Dr. Lester J. Palmer that a survey be made of life insurance companies which underwrite policies for diabetics

Careful consideration was given by the Committee on Statistics, at its meeting of June 2, to this proposal. It is presumed that this relates to applications by diabetics for new policies of "Ordinary" insurance (i. e., excluding Industrial and Group) subsequent to the diagnosis of their diabetes. The Committee was in accord with the basic idea of Dr. Palmer's proposal. The objectives, however, can best be attained without the use of a questionnaire to insurance companies at this time, partly because the practice of the large life insurance companies in this matter can be ascertained from published information available to the Committee, and it is probably of little or no consequence to the Association whether or not the companies insuring diabetics retain or reinsure the risks.

As regards the mortality experience on diabetics who are accepted for life insurance, it is not enough simply to ask companies whether or not their experience is satisfactory because this is neither objective enough nor would the results of a compilation of such answers give a really satisfactory picture of the situation. Evaluation of the insurance mortality experience is a technical procedure which can best be handled by the insurance companies themselves on the basis of an intercompany study. The proper method of obtaining this information will be discussed later.

Perhaps the most important question to be considered in this matter of insurance for diabetics is the relative success of diabetics in obtaining insurance after they apply. Inasmuch as a diabetic may apply several times before he is accepted, if at all, a compilation based upon inquiry of individual life insurance companies would not give a correct answer. Perhaps the best way to approach this problem is to send a questionnaire to a selected list of physicians who see a great many diabetics and who are called on in the course of the year to complete the forms required by the insurance companies before they will entertain an application from a diabetic. These physicians would be asked to inquire of patients whether or not they obtained the insurance applied for. Generally a period of four to six weeks after completion of the form submitted to the company is enough to allow before follow-up.

The Committee on Statistics recommends that this method be tried. It would suffice to obtain information on 1,000 diabetics, and this number can be obtained through the cooperation of about 50 physicians. The information to be requested should be limited to essential items. In addition to the necessary identifying details, the following should be included:

Duration of diabetes, age at onset, present age, sex, insulin dosage.

If accepted for insurance: whether accepted on initial application; number of rejections before acceptance;

whether the policy was issued for full amount applied for; if less than full amount issued, specify what proportion or percentage of amount applied for.

If rejected for insurance: To how many companies was application made?

Optional: On a voluntary basis it would be worthwhile asking the actual sum applied for and the amount issued.

The Committee on Statistics further recommends these steps to obtain life insurance company mortality experience on insured diabetics, as defined above:

a. Communication of the Association's interest in the matter to the appropriate life insurance organizations: The Society of Actuaries, the Association of Life Insurance Medical Directors of America, and the American Life Convention—Medical Section.

b. As an alternative, the Chairman of this Committee be empowered to make the necessary inquiries because (1) he has had it in mind to do anyway and deferred it until enough time had elapsed for sufficient experience to accumulate; and (2) Dr. Sheridan, of the Committee, and he both have ready access to the responsible officers of the Associations mentioned above.

*Committee Recommendation for Statistical Program of the Association Administered by a Statistician on the Staff**

The Committee on Statistics has proposed from time to time that certain activities of a statistical nature should be conducted by the Association as an essential function of the organization. Such a program would fulfill certain needs of the Association and is in line with the practice of other major voluntary organizations in medicine and public health, for example, the American Cancer Society, the American Heart Association, the National Tuberculosis Association, and the National Foundation for Infantile Paralysis. Since even for these organizations the statistical program varies widely, it is proper that any such plan for the American Diabetes Association take into account its particular needs and mode of organization, as well as the modest budget which would be available for such an operation.

The Committee has made a preliminary exploration of the matter, and while it is not yet ready to formulate plans in any detail it expects to do so before the next meeting of the Council and report further on the matter then. It does, however, recommend that the Council provide funds for a program to be operated by a statistician on the Association's staff, with enough clerical and other help from other staff members, so that the cost of this operation initially will not exceed $10,000 to $12,000 annually. The initial activities of the statistician would be:

1. To compile and analyze available data on incidence, morbidity and mortality from diabetes, and such additional statistical information on the disease as will enable the office of the American Diabetes Association to reply directly to inquiries on these subjects.

2. To provide information on these subjects to the Affiliates of the Association.

3. To assemble, analyze and interpret the data obtained in local Diabetes Detection Drives for use of the Association itself and for its Affiliates.

4. To conduct surveys of a limited character by the questionnaire method or otherwise. (The proposal of Dr. Palmer, which is considered earlier, is a good example of one of the functions of the proposed staff statistician.)

HERBERT MARKS, *Chairman*
ALEXANDER MARBLE, M.D.
JOYCE T. SHERIDAN, M.D.
HUGH L. C. WILKERSON, M.D.

*Referred by the Council to the Executive Committee.

SIXTEENTH ANNUAL MEETING

The next Annual Meeting of the American Diabetes Association will be held in Chicago, June 9-10, 1956, prior to the Annual Session of the American Medical Association, June 11-15. As previously announced, The Drake will serve as headquarters hotel, and a number of guest rooms will be available. An announcement of the meeting, together with a hotel reservation card, has been sent to all members of the Association, who are urged to make their reservations promptly. Please note that the hotel information cards which were mailed in the spring of the year were for survey purposes only. It is essential that members fill out and send directly to The Drake the reservation card which accompanies the announcement. Additional reservation cards may be secured by writing to the National Office.

SCIENTIFIC PROGRAM

Physicians and other scientists are invited by John A. Reed, M.D., Chairman of the Committee on Scientific Programs, to submit abstracts of papers which they would like to present at the Scientific Sessions.

Persons interested are requested to submit ten copies of the abstracts to facilitate review of the material by the Committee. Since a great number of abstracts will be at hand for the Committee to consider, they should be submitted as promptly as possible.

FOURTH STUDENT-INTERN ESSAY CONTEST

The American Diabetes Association for the fourth year is sponsoring a Student-Intern Essay Contest open to medical students, interns and physicians within two years after graduation from medical school. Any subject relating to diabetes and basic metabolic problems may be selected.

Two awards will be made again this year. A prize of $250 to the author or authors of the best paper reporting original laboratory research or clinical study is made possible through the generosity of the St. Louis Diabetes Association. An additional prize of $50 will be awarded for the best review article or case report.

Members of the Association and subscribers to DIABETES are requested to encourage medical students and interns in their schools and hospitals to enter the contest. Manuscripts, typewritten with double-spacing, should be submitted to the Editorial Office of DIABETES: *The Journal of the American Diabetes Association,* 1 East 45th St., New York 17, N. Y.

The papers will be reviewed by members of the Editorial Board who, in selecting the best papers, will consider the value of the material and the method of presentation.

NEW MEMBERS

The following Active Members were elected as of Nov. 1 and Dec. 1, 1955:

California
Fitch, Donald R. — Glendale
Johnson, Byron H. — Fresno

Delaware
Kaminsky, Aaron L. — Wilmington

Iowa
Gilfillan, Edwin O. — Bloomfield

Kansas
Page, Ruth — Wichita
Wilen, Carl J. W. — Manhattan
Wright, Lennel I. — Wichita

Louisiana
Buttross, David, Jr. — Lake Charles

Massachusetts
Quinn, Milton J. — Winchester

Minnesota
Rawls, Thompson T. — Rochester

Missouri
Burns, Thomas Wade — Columbia
Fox, Robert E. — St. Louis

New Jersey
Barnert, Morris — Irvington
Lukens, David Hellyer — Belmar
Simkin, Abraham — Passaic

New York
Slepian, Alexander — Niagara Falls

Ohio
Marcovich, Abraham W. — Dayton

Pennsylvania
Barrison, Wm. J., Jr. — Bloomsburg
Beem, John Raymond — Lansdale
Packer, Robert M., Jr. — Abington

Texas
Blount, Robert — Fort Sam Houston

OTHER COUNTRIES

Sweden
Ljungberg, Stellan — Stockholm

Switzerland
Rilliet, Bernard M. — Geneva

The following Associate Member was elected as of Nov. 1, 1955:

California
Cooley, Mrs. Alfaretta Johnson — Los Angeles

News Notes

TRAINING COURSES IN DIABETES

The Public Health Service, U.S. Department of Health, Education, and Welfare, will offer these training courses in diabetes control during 1956: Patient Education in Diabetes, February 27-March 2; Nursing Aspects of a Diabetes Program, March 19-23; The Clinical and Community Approach to Diabetes, April 23-27; Nutritional Aspects of a Diabetes Program, May 21-25; The Clinical and Community Approach to Diabetes, October 1-5.

The courses will be conducted at the Diabetes Field Research and Training Unit, Boston, Massachusetts. They are designed for physicians, public health administrators, nurses, dietitians, nutritionists, social workers, health educators and medical technologists. There is no fee for registration or tuition. Interested persons may obtain further information by writing to U.S. Public Health Service, Diabetes Field Research and Training, 639 Huntington Ave., Boston 15, Mass.

PERSONALS

BERNARDO A. HOUSSAY, M.D., Nobel Prize winner, has been reinstated as Professor and Director of the Physiological Institute in Buenos Aires, Argentina. He was discharged from this post for disagreeing with former President Peron's education policies. Dr. Houssay is an Honorary Member of the American Diabetes Association and a foreign consulting editor of DIABETES.

HENRY B. MULHOLLAND, M.D., immediate Past President of the American Diabetes Association, has been appointed chairman of a new committee on geriatrics of the American Medical Association's Council on Medical Service. Dr. Mulholland also serves as Vice Chairman of that Council. Among members of the committee is EDWARD L. BORTZ, M.D., ADA Councilor and Past President of the AMA.

OBITUARIES

CHARLES HENRY ARMENTROUT, M.D., Asheville, North Carolina, died recently at the age of 47. Dr. Armentrout, whose practice was limited to internal medicine, was a graduate of the Medical College of Virginia (1931). A member of the Active Staff of St. Joseph's Hospital, he was also Senior Consultant in Medicine, U. S. Veterans Administration Hospital (Oteen), and at the time of his death Chief of the Department of Medicine of Memorial Mission Hospital. In addition to his membership in the American Diabetes Association (1948), Dr. Armentrout was a member of the Association of Military Surgeons of the United States, a charter member and Vice President of the North Carolina Society of Internists, a Diplomate of the American Board of Internal Medicine and a Fellow of the American College of Physicians. Entering the Navy in 1942, he saw active service in both Atlantic and Pacific areas, and was the recipient of two unit citations and the Purple Heart. He was discharged as Lieutenant Commander in 1945.

COLONEL C. B. ICASIANO, MC, Santa Cruz, Manila, Philippines, died on March 15, 1955, in Walter Reed Hospital, Washington, D. C. Born in 1907 at San Roque, Cavite, Dr. Icasiano was a graduate of the College of Medicine, University of Philippines. He served an internship at the Philippine General Hospital and a residency in the Department of Medicine, Philippine General Hospital. Dr. Icasiano was Chief of Medicine at V Luna General Hospital (AFP), and a faculty member of the Colleges of Medicine at the University of Santo Tomas and Manila Central University. A member of the American Diabetes Association since 1952, he limited his practice to internal medicine.

JOSEPH SKWIRSKY, M.D., Newark, New Jersey, who died suddenly on Sept. 15, 1955, was born in Russia in 1893. He came to the United States when he was nineteen years of age, and obtained his premedical college education at the University of Missouri. Dr. Skwirsky received his degree in medicine from New York University and Bellevue Medical College in 1923. Following an internship at Newark (New Jersey) Beth Israel Hospital, he practiced internal medicine in Newark until his death. His postgraduate training included study at the University of Minnesota, the Mayo Clinic, and at Mt. Sinai and the Goldwater Memorial Hospitals in New York.

A former President of the New Jersey Diabetes Association and Chairman of its Clinical Society, Dr. Skwirsky was Attending Physician at the Newark Beth Israel Hospital and Chief of its Diabetes Clinic. He became a member of the American Diabetes Association in 1941, and was also a member of the American Academy of Allergy, a Diplomate of the American Board of Internal Medicine, and a Fellow of the American College of Physicians. He is survived by his wife and daughter.

SUBJECT INDEX

This index covers all reading matter in DIABETES. Most entries refer to material in the ABSTRACTS; entries marked with an asterisk (*) indicate articles which appeared in full in DIABETES during 1955. The author index appears on Page 528.

B

C

E

I

M

N

O

P

Q

R

S

T

Errata

p. 70 Rifkin, Harold. In second line insert *in* before *a*.

p. 150 Read, W. O., & Fodden, H. A. In tenth line the word *insulin* should be *glucose*.

p. 153 Urteaga B. Oscar, & Peralta, Aurelio. Author's name should read *Urteaga, B. Oscar*.

p. 201 Hubble, Douglas. In second column, tenth line, *hyperclycemic* should read *hyperglycemic*.

p. 240 Nelson, H. B., & others. In second column, seventeenth line, *therapy* should read *thereby*. In eighteenth line, *by* should be changed to *the*.

p. 306 Mulholland, Henry B. In second column, thirty-third line, *Is* at beginning of sentence should read *It*.

p. 319 Chaikoff, I. L. In fifteenth line insert *a* before the word *primary*. In sixteenth line, insert the word *effect* before *due*.

p. 324 Robel, G. In sixth line, the word *pancreas* should end a sentence. Delete the words *and that* following the word *pancreas*. The word *It* should start a new sentence.

p. 354 Korp, W., & LeCompte, P. M. In nineteenth line, the word *mineral* should read *minute*.

p. 374 Maclean, N., & Ogilvie, R. F. In second column, twentieth line, insert *characteristic* after *recessive*.

p. 415 Queries and Minor Notes (*Woodhull, Ill.*). In third line, *hypoglucemia* should read *hypoglycemia*.

AUTHOR INDEX

In this Index are the names of the authors of articles which have appeared in DIABETES and those whose articles have been abstracted in the Journal during 1955. The asterisk (*) preceding the page reference indicates that the article appeared in full in DIABETES.

For subject index see page 504.

S

T

U

V

W

Y

Z

Book Reviewers

Frank N. Allan, M.D., Boston
Edward L. Bortz, M.D., Philadelphia
Romeo Boucher, M.D.,* Montreal
Arthur R. Colwell, M.D., Chicago
Jerome W. Conn, M.D., Ann Arbor
Garfield G. Duncan, M.D., Philadelphia
Peter H. Forsham, M.D., San Francisco
George M. Guest, M.D., Cincinnati
Reed Harwood, M.D., Boston
*Guest book reviewer, 1955.

Blair Holcomb, M.D., Portland, Oregon
Alexander Marble, M.D., Boston
Rosemary Murphy, M.D., Boston
Lester J. Palmer, M.D., Seattle
Herbert H. Pollack, M.D., New York
Henry T. Ricketts, M.D., Chicago
George Schmitt, M.D., Miami
Penn G. Skillern, M.D., Cleveland
Randall G. Sprague, M.D., Rochester, Minnesota
Russell M. Wilder, M.D., Rochester, Minnesota

DIABETES

The Journal of the American Diabetes Association

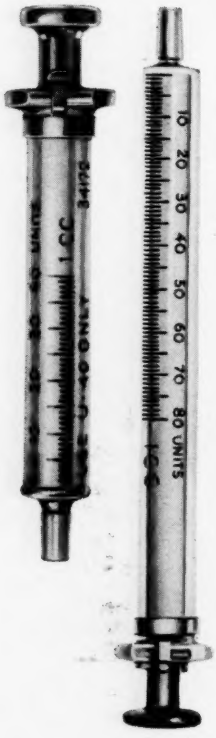
KARL PETREN

VOLUME 4, NUMBER 2

MARCH-APRIL 1955

for maximum convenience and ease of self-injection

B-D DIABETIC EQUIPMENT



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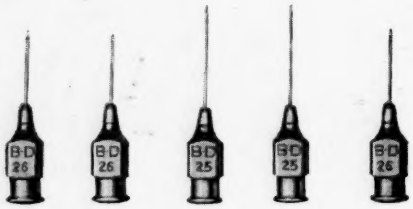
B-D Needles: Assure easy penetration—minimize seepage and afterpain—precision ground for greatest keenness, uniformity and safety.



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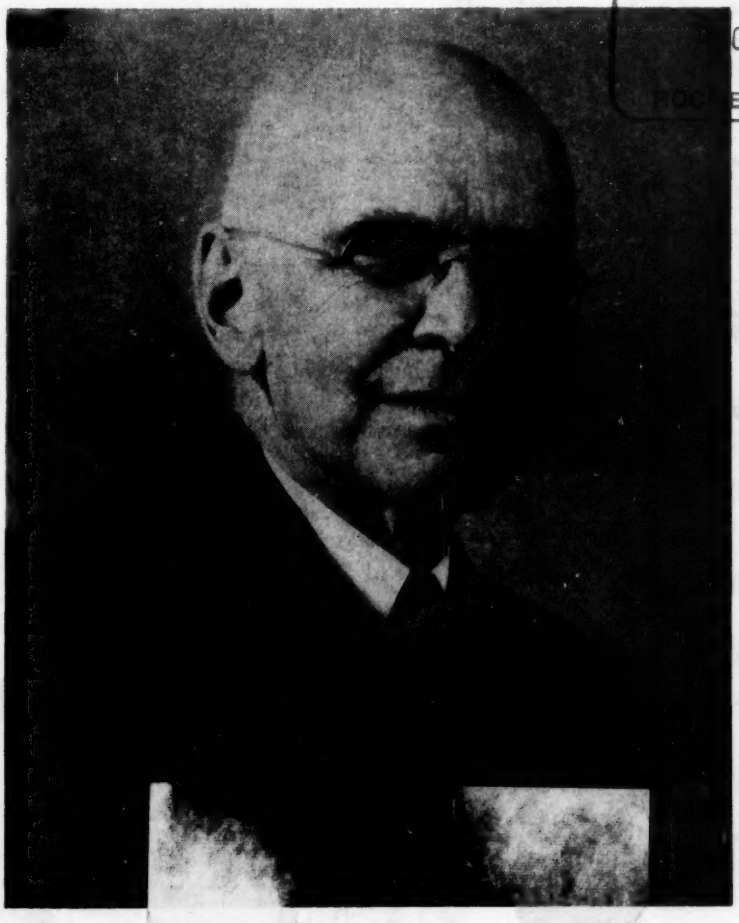
DIABETES

The Journal of the American Diabetes Association



ELLIOTT P. JOSLIN

VOLUME 4, NUMBER 3

MAY-JUNE 1955

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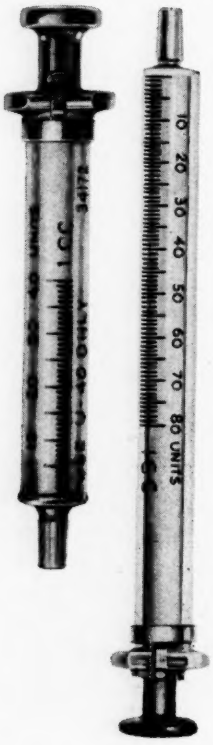

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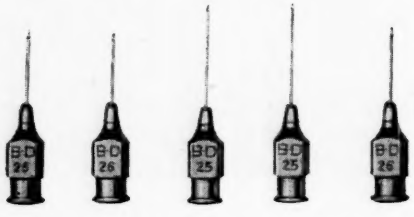

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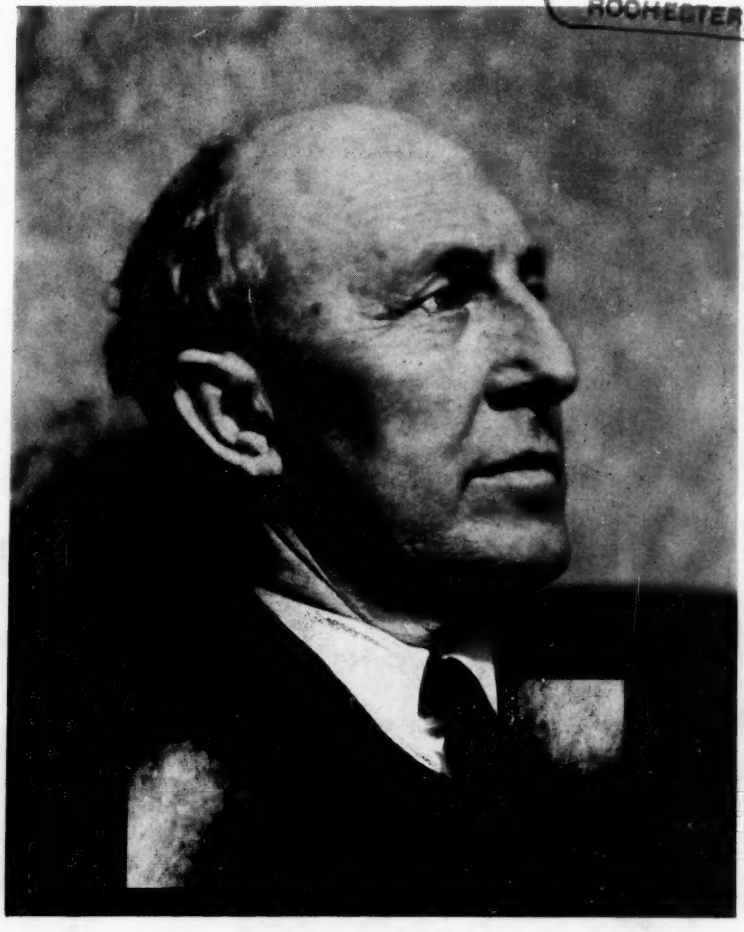
DIABETES

The Journal of the American Diabetes Association



ROBERT R. BENSLEY

VOLUME 4, NUMBER 4

JULY-AUGUST 1955

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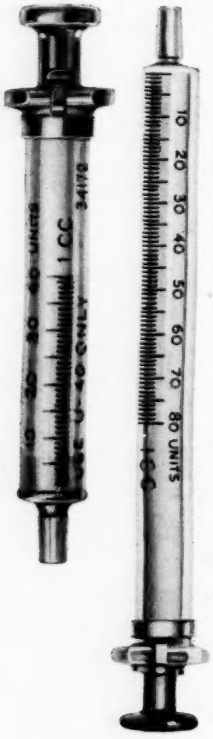

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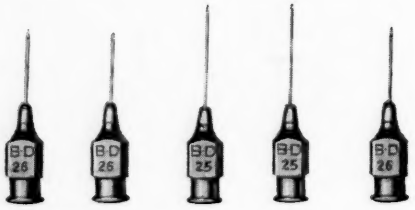

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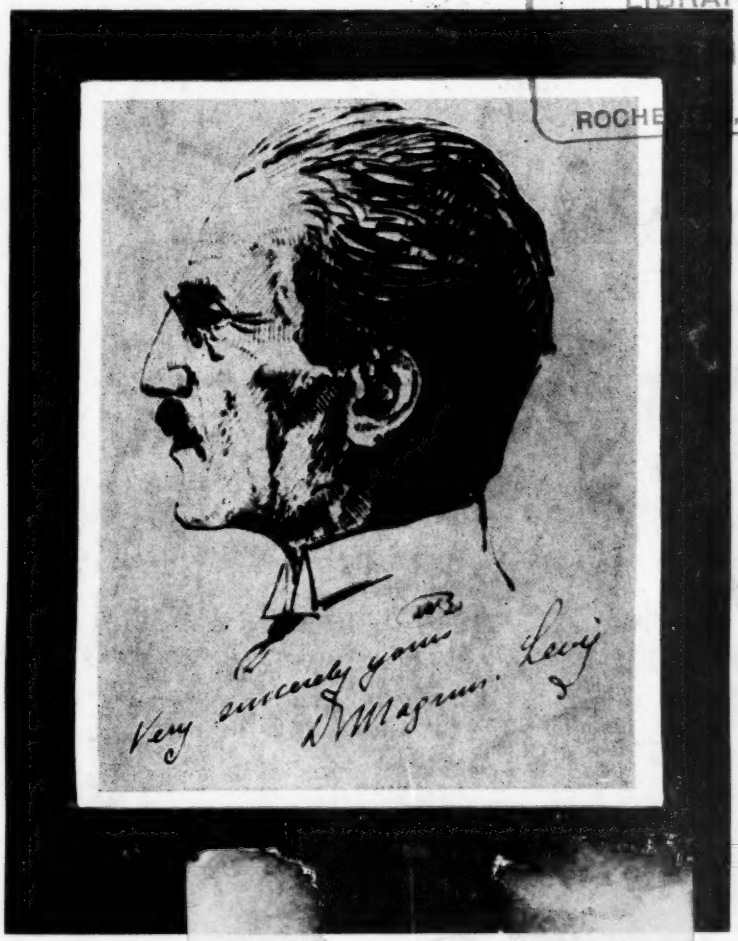
The Journal of the American Diabetes Association



ADOLF MAGNUS-LEVY

VOLUME 4, NUMBER 5

SEPTEMBER-OCTOBER 1955

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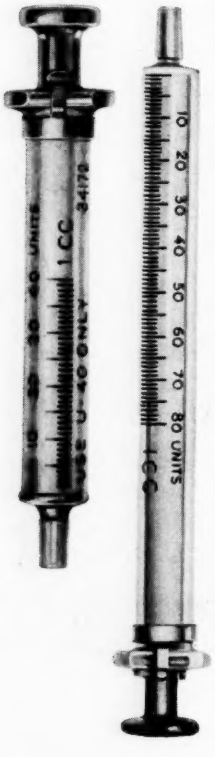

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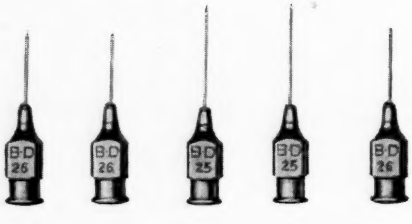

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DIABETES

The Journal of the American Diabetes Association

J. J. R. MACLEOD

VOLUME 4, NUMBER 6 NOVEMBER-DECEMBER 1955

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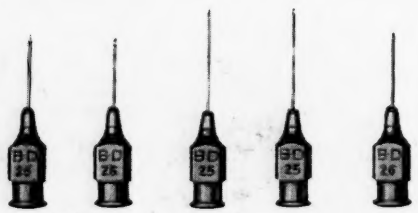

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